Fall risk and medication

New methods for the assessment of risk factors
in commonly used medicines

Judith Hegeman

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General introduction

Falls and medication

One-third of the elderly aged 65 years and older falls at least once a year [1,2]. About 20-30% of them gets injured in such a way that they lose mobility and independence and are at a greater risk of early death [2,3]. In the Netherlands only, each year about 99000 elderly visit the emergency department of a hospital after a fall incident and the direct medical costs of fall-related injuries in the elderly is on average 6900 per casualty [4]. Hence, not only do accidental falls have an impact on the affected individual, they have become a major socio-economic problem as well [5]. Therefore, many researchers focused on fall risk factors, and the reduction or even the prevention of falls in the elderly [2,6-10].

Many epidemiological studies showed that medication use is an important risk factor for accidental falls [2,11-14]. Two aspects were shown to play a major role: 1) the kind of medication [11,12,15-17], and 2) the number of medications that is taken (polypharmacy = concurrent use of several (>4) drugs [18]) [18-21]. Particularly psychotropic and cardiovascular drugs, diuretics and some analgesics are found to add to an increased fall risk [11,12,15,18,22-26]. These drugs are considered to be risk-drugs due to commonly reported central nervous system (CNS) adverse effects. It seems fairly self-evident that effects such as sleepiness, dizziness and drowsiness could underlie accidental falls. This view is enhanced by a warning put in leaflets or even as obligatory medication warning labels. That warning implies that if a user experiences CNS adverse effects that affect mental or physical capabilities, it is discouraged to engage oneself in activities such as driving a car or operating machinery. Similar to such activities, quick and adequate postural responses are also necessary to prevent falling during standing or walking. Risk-drugs for falling should therefore prescribed restrictedly, at the smallest doses and for the shortest time possible. Previous research has indeed shown that withdrawal of fall-risk-increasing drugs or even just lowering the dose significantly reduced fall risk in an elderly population [9]. Hence, a thorough evaluation of the medication use could have a major (positive) impact on the individuals' fall risk. However, sensitive methods to quantitatively investigate the fall risk of single medications are still lacking. In addition, only poor knowledge exists on which fall-related skills are possibly affected by medication. Therefore this thesis aimed to gain insight into the influence of commonly used medicines on fall-related skills. This insight could be useful to prevent accidental falls by more careful prescription of risk drugs and to provide a user with better information regarding possible fall risk after intake of such a risk-drug.

Skills related to falling

Studies in various populations showed that accidental falls often are associated with deficiencies in a number of skills such as balance control, response to sudden events and dual-tasking during gait. Proper balance control is essential to prevent falling. It is rather easy to assess possible impairments in balance control using quiet stance tasks under various conditions. Tasks measuring quiet stance with eyes open or closed are mostly used in the assessment of the effects of medication on balance control. However, it seems likely that these tasks might not be sensitive enough to detect possible subtle effects. Challenging and demanding balance tasks such as one-legged stance or stance on a compliant surface could be more suitable for this and should therefore be added to the so-called conventional tasks mentioned above.

The ability to respond quickly and adequately to sudden events is another skill related to falls. This skill is often assessed using classical manual reaction time tasks. However, falling or tripping is mostly caused by slowed and/or inadequate responses to suddenly appearing obstacles during gait. Hence, it was suggested that the assessment of reaction times during walking would be more appropriate in view of accidental falls. Therefore, an obstacle avoidance task was developed [27,28]. This task has already been used to measure the effects of startle, aging, or fall-prevention programs [29-31], but up till now it was never used to assess the effects of medication on obstacle avoidance reactions.

A third important skill related to falls is the ability to concurrently perform both a motor task and a secondary cognitive task (dual-tasking) [28,32]. In the last two decades, the effects of dual-tasking on quiet stance and normal gait have been extensively studied (for a review see Woollacott and Shumway-Cook [33]), but the findings were not always consistent. In addition, often rather crude outcomes (e.g. gait velocity or number of errors on the secondary task) were used to evaluate the effects of dual-tasking. Moreover, knowledge on the effects of dual-tasking on less automatic gait such as limping or avoiding obstacles is limited, but might be more relevant in understanding the relation between dual-tasking and falls.

Outline of this thesis

The first part of this thesis focuses on the composition of a set of tests which makes it possible to assess even subtle effects of medication on fall-related skills. Therefore, this part is methodological of nature.

Chapter 2 describes the study in which it was investigated whether a time-critical obstacle avoidance task is sensitive enough to assess the effects of alcohol, a substance generally known to affect gait, on obstacle avoidance skills. Participants had to avoid suddenly appearing obstacles while walking on a treadmill at a fixed velocity of 3 km/h. Obstacle avoidance performance was quantified by determining success rates and avoidance response times and this was compared between three alcohol concentration levels.

Chapter 3 describes the effect of a secondary cognitive task on gait under difficult circumstances, limping in particular. In this study participants walked on a split-belt treadmill with symmetric (2 km/h) and asymmetric (2 km/h vs. 4 km/h and 2 km/h vs. 6 km/h) belt speeds both with and without a concurrent cognitive task. For this task the participants listened to the words "high" or "low" in Dutch, presented in either a high or low pitch, and indicated verbally which tone was presented as quickly as possible. Verbal reaction times, stance phase and support phase proportions were compared between walking conditions.

Chapter 4 presents the study which investigated dual-task interference during a time-critical obstacle avoidance task in healthy seniors. The obstacle avoidance task described in Chapter 2 was combined with the secondary cognitive task described in Chapter 3. For the primary task, success rates and avoidance reactions were compared between single- and dual-task conditions. Performance on the secondary task was quantified by using composite scores (= (accuracy/ verbal response time(ms)) x100) [34] and was compared between three instants of the obstacle avoidance task (prior, during and just after obstacle crossing).

In short, this first part of the thesis supports the use of a time-critical obstacle avoidance task and a secondary cognitive task to measure the effects of medication on these fall-related skills.

In the second part of this thesis the above mentioned tasks are combined with more conventional methods of assessing fall-related skills. Hereby we aimed to gain insight into the fall risk after use of drugs frequently prescribed as a treatment for two important chronic conditions in the elderly: rheumatic and psychosocial diseases [35]. Two drug classes supposed to put the user at an increased risk of

falling were selected for the experiments; NSAIDs (non-steroidal anti-inflammatory drugs) and SSRIs (selective serotonin reuptake inhibitors) in particular.

In Chapter 5 a systematic literature review is given on NSAIDs and the risk for accidental falls in the elderly. This review showed that there is some evidence for an increased fall-risk with NSAIDs and that there was room for an experimental study on the effects of this kind of medication on fall-related skills in elderly. It was decided to use both conventional methods (Chapter 6) and new methods (as described above, Chapter 7).

Chapter 6 describes the outcomes of a RCT (randomized controlled trial) in which the effect of a NSAID on postural balance and manual reaction time, two important predictors for accidental falls, was assessed in healthy seniors. This study served two purposes. A first aim was to bridge the gap to the conventional tasks and to existing knowledge on psychomotor effects of drugs in particular. The second aim was to expand the set of conventional quiet stance tasks with stance tasks that were more challenging. In this double-blind placebo-controlled study, the performance on all quiet stance tasks as well as the manual reaction time tasks was compared between the three experimental conditions (indomethacin (NSAID), placebo, and baseline).

In Chapter 7 the new methods presented in the first part of this thesis are used to test the effects of a NSAID. The effect of indomethacin on the ability to avoid suddenly appearing obstacles was studied during walking, with or without simultaneous performance of a secondary cognitive task. The consequences of such a combination with regard to accidental falls was illustrated using similar performance outcomes as described in Chapter 4.

In Chapter 8 all above mentioned methods (a time-critical obstacle avoidance task, an extensive set of quiet stance tasks, and manual reaction time tasks) were applied to assess the effect of paroxetine, a commonly used SSRI [36], on these skills related to falls. For all tasks, the performance of senior long term (>90 days) paroxetine users was compared with that of healthy senior individuals.

Finally, in Chapter 9 the main findings and conclusions of this thesis are discussed and suggestions for future research are given.

References

1. Tinetti ME, Speechley M, Ginter SF: **Risk factors for falls among elderly persons living in the community.** *N Engl J Med* 1988, **319:** 1701-1707.
2. Rubenstein LZ: **Falls in older people: epidemiology, risk factors and strategies for prevention.** *Age Ageing* 2006, **35 Suppl 2:** ii37-ii41.
3. Alexander BH, Rivara FP, Wolf ME: **The cost and frequency of hospitalization for fall-related injuries in older adults.** *Am J Public Health* 1992, **82:** 1020-1023.
4. Consument en Veiligheid. Letsellastmodel 2009. 2011.
5. Stevens JA, Corso PS, Finkelstein EA, Miller TR: **The costs of fatal and non-fatal falls among older adults.** *Inj Prev* 2006, **12:** 290-295.
6. Berg WP, Alessio HM, Mills EM, Tong C: **Circumstances and consequences of falls in independent community-dwelling older adults.** *Age Ageing* 1997, **26:** 261-268.
7. Campbell AJ, Robertson MC: **Implementation of multifactorial interventions for fall and fracture prevention.** *Age Ageing* 2006, **35 Suppl 2:** ii60-ii64.
8. Lord SR, Menz HB, Tiedemann A: **A physiological profile approach to falls risk assessment and prevention.** *Phys Ther* 2003, **83:** 237-252.
9. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ: **Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study.** *Br J Clin Pharmacol* 2007, **63:** 232-237.
10. Weerdesteyn V, Rijken H, Geurts AC, Smits-Engelsman BC, Mulder T, Duysens J: **A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly.** *Gerontology* 2006, **52:** 131-141.
11. Cumming RG, Miller JP, Kelsey JL, Davis P, Arfken CL, Birge SJ *et al.*: **Medications and multiple falls in elderly people: the St Louis OASIS study.** *Age Ageing* 1991, **20:** 455-461.
12. Hartikainen S, Lonnroos E, Louhivuori K: **Medication as a risk factor for falls: critical systematic review.** *J Gerontol A Biol Sci Med Sci* 2007, **62:** 1172-1181.
13. Kelly KD, Pickett W, Yiannakoulias N, Rowe BH, Schopflocher DP, Svenson L *et al.*: **Medication use and falls in community-dwelling older persons.** *Age Ageing* 2003, **32:** 503-509.
14. Monane M, Avorn J: **Medications and falls. Causation, correlation, and prevention.** *Clin Geriatr Med* 1996, **12:** 847-858.
15. Koski K, Luukinen H, Laippala P, Kivela SL: **Physiological factors and medications as predictors of injurious falls by elderly people: a prospective population-based study.** *Age Ageing* 1996, **25:** 29-38.
16. Elley CR, Robertson MC, Kerse NM, Garrett S, McKinlay E, Lawton B *et al.*: **Falls Assessment Clinical Trial (FACT): design, interventions, recruitment strategies and participant characteristics.** *BMC Public Health* 2007, **7:** 185.
17. Robbins AS, Rubenstein LZ, Josephson KR, Schulman BL, Osterweil D, Fine G: **Predictors of falls among elderly people. Results of two population-based studies.** *Arch Intern Med* 1989, **149:** 1628-1633.
18. Ziere G, Dieleman JP, Hofman A, Pols HA, van der Cammen TJ, Stricker BH: **Polypharmacy and falls in the middle age and elderly population.** *Br J Clin Pharmacol* 2006, **61:** 218-223.
19. Moylan KC, Binder EF: **Falls in older adults: risk assessment, management and prevention.** *Am J Med* 2007, **120:** 493-496.
20. Russell MA, Hill KD, Blackberry I, Day LL, Dharmage SC: **Falls risk and functional decline in older fallers discharged directly from emergency departments.** *J Gerontol A Biol Sci Med Sci* 2006, **61:** 1090-1095.
21. van HS, Wyers CE, Dagnelie PC, van Dongen MC, Willems G, Brink PR *et al.*: **Risk of falling in patients with a recent fracture.** *BMC Musculoskelet Disord* 2007, **8:** 55.
22. Leipzig RM, Cumming RG, Tinetti ME: **Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs.** *J Am Geriatr Soc* 1999, **47:** 30-39.
23. Leipzig RM, Cumming RG, Tinetti ME: **Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs.** *J Am Geriatr Soc* 1999, **47:** 40-50.
24. Kerse N, Flicker L, Pfaff JJ, Draper B, Lautenschlager NT, Sim M *et al.*: **Falls, depression and antidepressants in later life: a large primary care appraisal.** *PLoS One* 2008, **3:** e2423.
25. Thapa PB, Gideon P, Fought RL, Ray WA: **Psychotropic drugs and risk of recurrent falls in ambulatory nursing home residents.** *Am J Epidemiol* 1995, **142:** 202-211.

26. Yip YB, Cumming RG: **The association between medications and falls in Australian nursing-home residents.** *Med J Aust* 1994, **160:** 14-18.
27. Schillings AM, van Wezel BM, Mulder T, Duysens J: **Muscular responses and movement strategies during stumbling over obstacles.** *J Neurophysiol* 2000, **83:** 2093-2102.
28. Weerdesteyn V, Schillings AM, van Galen GP, Duysens J: **Distraction affects the performance of obstacle avoidance during walking.** *J Mot Behav* 2003, **35:** 53-63.
29. Queralt A, Weerdesteyn V, van Duijnhoven HJ, Castellote JM, Valls-Sole J, Duysens J: **The effects of an auditory startle on obstacle avoidance during walking.** *J Physiol* 2008, **586:** 4453-4463.
30. Weerdesteyn V, Nienhuis B, Duysens J: **Advancing age progressively affects obstacle avoidance skills in the elderly.** *Hum Mov Sci* 2005, **24:** 865-880.
31. Smulders E, van LW, Laan R, Duysens J, Weerdesteyn V: **Does osteoporosis predispose falls? a study on obstacle avoidance and balance confidence.** *BMC Musculoskelet Disord* 2011, **12:** 1.
32. Faulkner KA, Redfern MS, Cauley JA, Landsittel DP, Studenski SA, Rosano C *et al.*: **Multitasking: association between poorer performance and a history of recurrent falls.** *J Am Geriatr Soc* 2007, **55:** 570-576.
33. Woollacott M, Shumway-Cook A: **Attention and the control of posture and gait: a review of an emerging area of research.** *Gait Posture* 2002, **16:** 1-14.
34. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM: **Dual-tasking effects on gait variability: the role of aging, falls, and executive function.** *Mov Disord* 2006, **21:** 950-957.
35. www.sfk.nl. 2009.
36. www.gipdatabank.nl. 2011.

2

Even low alcohol concentrations affect obstacle avoidance reactions in healthy senior individuals

Hegeman J, Weerdesteyn V, van den Bemt BJ, Nienhuis B, van Limbeek J, Duysens J: **Even low alcohol concentrations affect obstacle avoidance reactions in healthy senior individuals.** *BMC Res Notes* 2010, **3:** 243.

Abstract

Alcohol is a commonly used social drug and driving under influence is a well-established risk factor for traffic accidents. To improve road safety, legal limits are set for blood alcohol concentration (BAC) and driving, usually at 0.05% (most European countries) or 0.08% (most US states, Canada and UK). In contrast, for walking there are no legal limits, yet there are numerous accounts of people stumbling and falling after drinking. Alcohol, even at these low concentrations, affects brain function and increases fall risk. An increased fall risk has been associated with impaired obstacle avoidance skills. Low level BACs are likely to affect obstacle avoidance reactions during gait, since the brain areas that are presumably involved in these reactions have been shown to be influenced by alcohol. Therefore we investigated the effect of low to moderate alcohol consumption on such reactions. Thirteen healthy senior individuals (mean(SD) age: 61.5(4.4) years, 9 male) were subjected to an obstacle avoidance task on a treadmill after low alcohol consumption. Fast stepping adjustments were required to successfully avoid suddenly appearing obstacles. Response times and amplitudes of the m. biceps femoris, a prime mover, as well as avoidance failure rates were assessed. After the first alcoholic drink, 12 of the 13 participants already had slower responses. Without exception, all participants' biceps femoris response times were delayed after the final alcoholic drink (avg±sd:180±20ms; $p<0.001$) compared to when participants were sober (156±16ms). Biceps femoris response times were significantly delayed from BACs of 0.035% onwards and were strongly associated with increasing levels of BAC ($r=0.6$; $p<0.001$). These delays had important behavioural consequences. Chances of hitting the obstacle were doubled with increased BACs. The present results clearly show that even with BACs considered to be safe for driving, obstacle avoidance reactions are inadequate, late, and too small. This is likely to contribute to an increased fall risk. Therefore we suggest that many of the alcohol-related falls are the result of the disruptive effects of alcohol on the online corrections of the ongoing gait pattern when walking under challenging conditions.

Introduction

Alcohol is a commonly used social drug and driving under influence is a well-established risk factor for traffic accidents [1]. To improve road safety, legal limits are set for blood alcohol concentration (BAC) and driving, usually at 0.05% (most European countries) or 0.08% (most US states, Canada and UK). For other tasks than driving, however, it remains unclear whether these BACs also reflect appropriate safety limits. Recent research showed that among working-aged people, ingestion of alcohol in the previous 6 hours is strongly and consistently related to falls at home resulting in admission to hospital or death, even with low levels of alcohol consumption [2]. The public health impact of falls is substantial and concomitant costs are growing [2,3]. However, reducing alcohol intake is often not included in intervention strategies to prevent falls. Low alcohol intake is generally not deemed unsafe with regard to falls, but this was never investigated systematically. Accidental falls have been found to be associated with impaired obstacle avoidance skills [4]. To prevent tripping, accurate goal-directed reactions are required to avoid sudden obstacles in the travel path. In previous work we have observed that an increased percentage of obstacles that were hit ("obstacle avoidance failures") is associated with the presence of smaller and later EMG responses in the prime movers (such as the m. biceps femoris) involved in the obstacle avoidance reaction [5,6]. From cat studies it is known that the parietal cortex and the cerebellum play an important role in this reaction [7,8]. Imaging studies have shown that acute alcohol administration significantly reduces brain glucose metabolism in these areas that are important for obstacle avoidance [9-11]. Hence, one would predict obstacle avoidance reactions during gait to be disturbed by alcohol ingestion. Therefore we investigated the effect of low to moderate alcohol consumption on such reactions in healthy senior individuals by means of an obstacle avoidance task.

It was hypothesized that obstacle avoidance reactions are already impaired at low BACs, and that the increases in the percentage of obstacles that were hit after alcohol consumption will be accompanied by delayed and decreased muscle responses in the m. biceps femoris.

Methods

Participants

Thirteen healthy senior individuals (mean(SD) age: 61.5 (4.4) years, 9 male) volunteered to participate in this study. None of the participants was, or used to be a habitual drinker. Inclusion criteria were absence of any known serious neurological, orthopaedic or cognitive dysfunction, and age between 50-70 years. Exclusion criteria were a bodyweight exceeding 100 kg or the use of (prescribed) medication(s) that could interfere with alcohol. As the experiment took place in the late afternoon, participants were instructed to just have an early light lunch (e.g. a sandwich), and not to drink caffeinated drinks in the 4 hours before arriving at the laboratory. Subjects were informed about the experimental procedure before they gave their written informed consent in accordance with the ethical standards of the Declaration of Helsinki. The protocol was approved by the ethical committee of the region Arnhem-Nijmegen.

Equipment and procedure

The participants were instructed to avoid obstacles while walking on a treadmill (ENRAF Nonius, type ENtred Reha) at a fixed velocity of 3 km/hr (Figure 1A), wearing their own comfortable shoes (no high heels). A wooden obstacle (measuring 40x30x1.5cm) with an embedded piece of iron was held by an electromagnet just above the treadmill surface. Its release could be triggered by the computer. The obstacle was always presented to the left foot. On both feet, three reflective markers (diameter 14 mm) were attached at heel, hallux and lateral malleolus. A single marker was placed on top of the obstacle. Marker positions were recorded by an 8-camera 3-D motion analysis system (Vicon®, Oxford Metrics, London, UK) at a sample rate of 100 Hz. The marker positions were processed in real time in order to determine the moment of obstacle release related to gait phase. The real time processing also enabled the experimenter to check online the foot position with respect to the obstacle, while the participants were instructed to walk at a fixed distance to the obstacle that was approximately 10 cm from the most anterior position reached by the toes in the swing phase. If they deviated more than 3 cm from this position, participants received verbal feedback to correct the distance to the obstacle. The obstacle was not released until a regular walking pattern was observed and until at least five unperturbed strides for the trial had been completed. Stride regularity was defined as a maximum difference of 50 ms between two consecutive strides. The obstacle

was dropped at one of three different phases of the step cycle (late stance (LSt,45-60% of the step cycle), early swing (ESw, 60-70%) or mid swing (MSw,70-85%)) to create different levels of difficulty to avoid the obstacle as time pressure increased (Figure 1B). Available response time (ART), the measure of time pressure, was defined as the time between obstacle release and the estimated moment of foot contact with the obstacle if no adjustment of the stride had been made [12]. The obstacle release phases corresponded with ARTs greater than 450 ms (LSt), 300-450 ms (ESw), and 150-300 ms (MSw). Ten obstacles in each of the three phases of the gait cycle were presented in random order during a series of 30 trials.

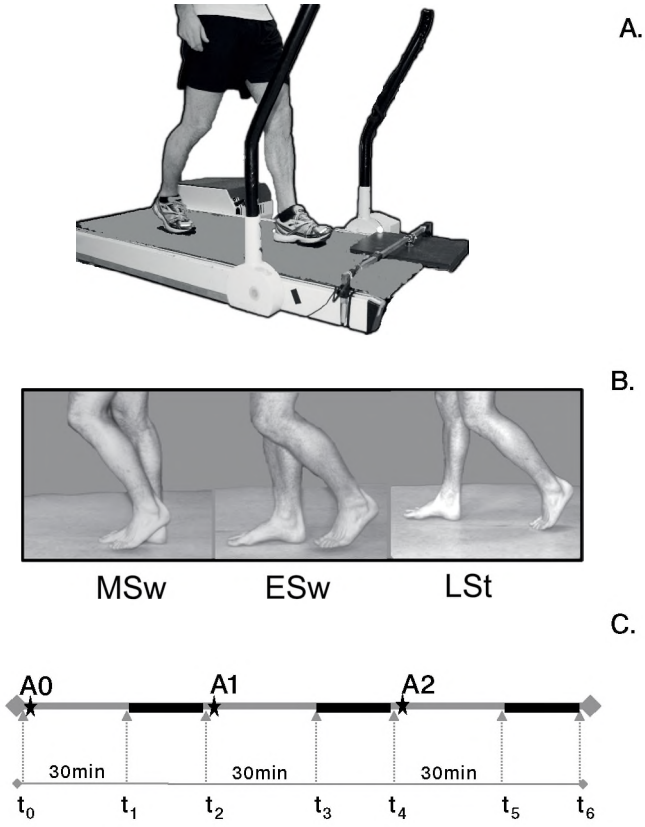
The participants were instructed to look at the obstacle, and step over it after its release. Stepping to the side was discouraged, and any contact of the left foot with the obstacle was defined as a failure. Since the m. biceps femoris (BF) is known to be the prime mover involved in the avoidance reaction [6], surface electromyography (EMG) data were collected from this muscle to assess response times. Self-adhesive Ag-AgCl electrodes (Tyco Arbo ECG) were placed approximately 2 cm apart and longitudinally on the belly of the muscle, according to European guidelines [13]. The EMG signals were sampled at 2400 Hz (ZeroWire®, Aurion S.r.l., Italy) and recorded synchronously with the marker data. Three series of 30 obstacle avoidance trials were performed, each 30 minutes after ingestion of a drink (Figure 1C). Subjects were informed that these drinks contained alcohol, and had to finish them within 10 minutes. The first (A0) was a placebo consisting of water mixed with orange juice (ratio 1:3) with a drop of vodka floated on top to give the scent of alcohol. The following two drinks (A1 and A2) each contained 40% vodka mixed with orange juice (ratio 1:3). We aimed to reach a BAC that was around the common legal limits for driving (0.05% for most European countries or 0.08% for most US states, Canada and UK) 30 minutes after A2, having used the Widmark formula [14] to adjust the alcohol dosage for the individual's gender and weight. A Dräger Alcotest® 7410 Plus com breathalyzer was used to determine the BAC before, during, and after the experimental task (Figure 1C). For safety reasons, all participants were taken home by a taxi after the experiment was finished.

Data analysis

Successful obstacle avoidance for each trial was scored. This was easily determined by two observers by eye, and by feedback from the participant. If there was any doubt about the successfulness, the marker data were checked

Figure 1 Methods

A. Experimental setup. **B.** Step cycle phases in which the obstacle was released. MSw = Mid Swing, ESw = Early Swing, LSt = Late stance. **C.** Protocol: assessment of BAC at t0-t6. A0: placebo, A1: first alcoholic drink, A2: second alcoholic drink. Solid black line: obstacle avoidance task.

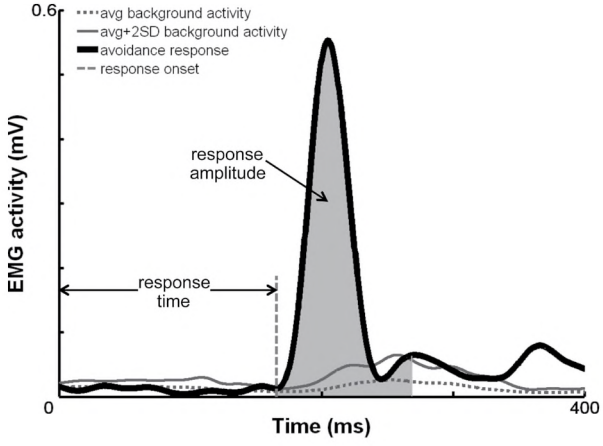


(this happened in less than 1% of the cases). As the primary outcome measure, failure rates (as defined by the number of failed trials divided by the total number of trials) were calculated for each alcohol condition and each step cycle phase. To assess the EMG responses, the EMG activity of the m. biceps femoris (BF) was full-wave rectified and lowpass filtered at 25 Hz (zero lag, 4th order Butterworth filter). Background EMG was calculated for each series separately as the average

BF activity over 25 control strides (i.e. the stride preceding that in which obstacle release occurred). For each participant and alcohol condition, BF response times were determined as the time between obstacle release and the moment at which BF activity exceeded the average control stride by at least 2 SDs for more than 30 ms (for example, see Figure 2). This was done with the help of a custom made computer algorithm (Matlab® software, version 7.4.0, The Mathworks Inc., US). Each trial for which a response time was calculated was visually checked for correct determination of the response onset. In about 2% of the trials the onsets were corrected. The onsets of the avoidance responses for each subject were averaged for each phase of obstacle release within each alcohol condition. The responses amplitude was calculated as the average amplitude during the 100 ms following the onset of the BF response [5,15]. The amplitudes were normalized with respect to the maximum average background activity during the whole step cycle in the A0 condition. A similar procedure was performed to calculate and normalize the average control stride activity in the 100 ms following the BF response onset.

Figure 2 Determination of response time and amplitude of the m. biceps femoris (BF)

Response time was defined as the time between obstacle release (set at the origin of the axes) and the moment where the BF activity exceeded the activity of the control stride + 2SD. Average response amplitude was calculated over 100ms after the onset of the response and normalized with respect to the average control stride activity.



Statistical analysis

To check whether within participants, the series were equally difficult in the three alcohol conditions, we compared the average ARTs in a repeated measures MANOVA (within-subjects factors: alcohol condition (A0, A1, A2); phase of obstacle release (LSt, ESw, MSw), α=0.05) with post-hoc pairwise comparisons. To identify the effect of BAC on avoidance failure rates we used a binary logistic regression with alcohol condition as categorical factor (A0 as reference category, α=0.05) in Egret® for Windows (version 2.0.31). A statistical model was fitted to the data of the MSw phase to predict the probability of a failure with increasing BAC for the most time critical situations.

For the analysis of EMG data, we used repeated measures MANOVAs with post-hoc pairwise comparisons to test for differences between the three alcohol conditions (within subjects-factor: A0, A1, A2; α=0.05) for average BF response times, normalized response amplitudes, and normalized background activity. The relationship between BF response time and BAC was assessed by means of bivariate correlation (Pearson Correlation Coefficient). One sample Students' t-test with bins of 0.005% BAC was used to determine the BAC from which the BF response time was significantly delayed. These analyses were carried out in SPSS® (version 12.0.1) with α set at 0.05. Means are presented with their standard errors (SE).

Pilot data indicated that the difference in obstacle avoidance response time after 2-3 standard alcoholic drinks was 20 ms (SD: 18 ms). To be able to identify a difference of 20 ms in the mean response time between A0 and A2, a sample size of 11 subjects would be needed in this repeated measures design (β=0.9, α=0.05).

Results

Before the start of the experiment, the BAC of each participant was 0.00%. After the final drink the BACs found ranged from 0.03% to 0.06%. Hence, we succeeded in our aim to reach BACs around or below common legal limits for driving (0.05% for most European countries or 0.08% for most US states, Canada and the UK). The series of the obstacle avoidance trials were equally difficult in the three alcohol conditions (A0, A1, and A2), as there were no significant main effects of alcohol condition on the average ARTs ($F_{2,1}$ =0.22, p=0.81).

Failures

Figure 3A shows the effect of alcohol on avoidance failure rates. Overall, the failure rate increased significantly from 4.5% (A0) to 8.8% (p<0.01) after

consumption of two alcoholic drinks. Figure 3A also demonstrates that in each alcohol condition most failures were made in the MSw phase ($p<0.01$, compared to late stance). Within this phase, the failure rate increased significantly with alcohol consumption, from 11.7% in A0, to 19.2% and 20.5% in A1 and A2, respectively ($p<0.01$, compared to A0). Moreover, the probability of a failure not only increased with higher BACs, but also with lower ARTs, which corresponded to the MSw phase (Figure 3B). Compared to the placebo condition, chances of hitting the obstacle almost doubled after the final alcoholic drink (odds ratio (95%CI) = 1.93 (1.17,3.18); $p=0.01$).

Figure 3 Effect of alcohol on failures

A. Failure rate per alcoholic condition for each step cycle phase separately, and in total. A0: placebo, A1: first alcohol, A2: second alcohol. (**$p<0.01$, compared to A0). **B.** Model of the probability of failing to avoid the obstacle with increasing blood alcohol concentrations for the most time critical situations.

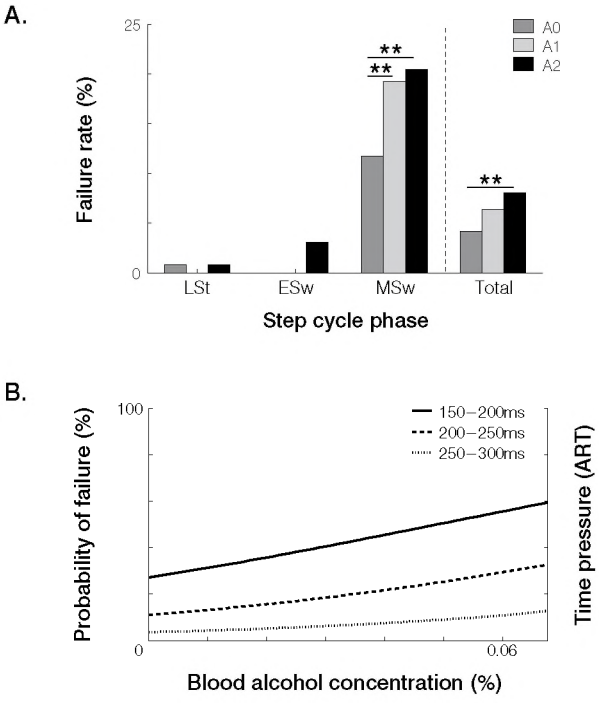
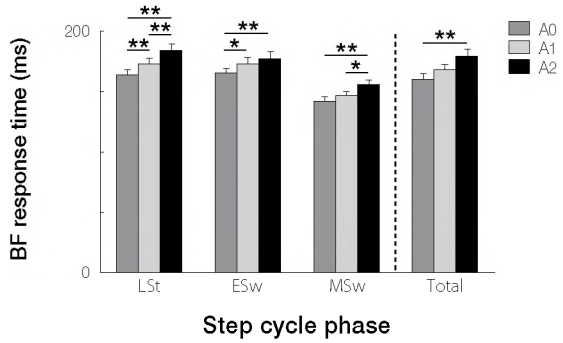


Figure 4 Effect of alcohol on BF response times for each step cycle phase separately, and in total

LSt=Late Stance, Esw=Early Swing, MSw=Mid Swing. A0: placebo, A1: first alcohol, A2: second alcohol. (*$p<0.05$, **$p<0.01$)



Response time

The results for BF response times, one of the proposed determinants of successful obstacle avoidance, are shown in Figure 4. Repeated measures MANOVA revealed a main effect of alcohol condition on overall BF response times ($F_{2,11}$=24.93, $p<0.001$), as well as for each phase of obstacle release separately (Table 1). After ingestion of 2 alcoholic drinks (mean±SD: 0.47±0.04 g alcohol/kg bodyweight), BF response times were delayed by 12% compared to when participants were sober (179±5.8 vs 160±4.7 ms, $F_{1,12}$=53.42, $p<0.001$) (Figure 4). From the data of the individual subjects (Figure 5) it can be seen that without exception, BF response times for all participants were delayed following A2. Furthermore, even after A1, 12 of the 13 participants already responded more slowly. The BF response times were significantly delayed from BACs of 0.035% upwards (t=18.05; p=0.003). There was a significant correlation between response time and level of BAC (r=0.6; $p<0.001$; Figure 5).

A significant effect of obstacle release phase on BF response times was also found. The LSt responses were significantly slower than those in ESw ($F_{1,12}$=52.65, $p<0.001$). In turn, ESw responses were again significantly slower than those in MSw ($F_{1,12}$=49.86, $p<0.001$).

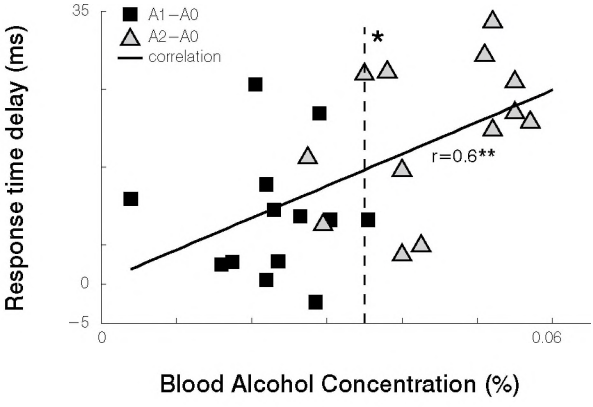
Table 1 Repeated measures MANOVA with within subjects contrast for BF response latencies

A0 = placebo, A1 = first alcohol, A2 = second alcohol, LSt = Late Stance, ESw = Early Swing, MSw = Mid Swing, Total = all trials, Diff = difference. Bold numbers indicate significance.

	LSt			ESw			MSw			Total		
	Diff(ms)	$F_{1,12}$	*p*	*Diff(ms)*	$F_{1,12}$	*p*	*Diff(ms)*	$F_{1,12}$	*p*	*Diff(ms)*	$F_{1,12}$	*p*
A0 vs A1	8.3	11.0	**0.006**	9.2	5.6	**0.036**	5.4	2.0	0.182	8.7	15.0	**0.002**
A1 vs A2	10.8	12.0	**0.005**	5.0	1.2	0.287	11.0	18.4	**0.001**	10.8	22.7	**0.000**
A2 vs A0	19.2	26.8	**0.000**	14.2	10.0	**0.008**	16.4	36.3	**0.000**	19.4	53.4	**0.000**

Figure 5 Individual delays in BF response times after the first (A1) and second (A2) drink as compared with the A0 condition

Each data point represents one subject in the corresponding alcohol condition. The solid line shows the correlation between BAC and the delay in response time (**$p<0.01$). The dashed line represents the BAC from whereon the delay is significant (*$p<0.05$).

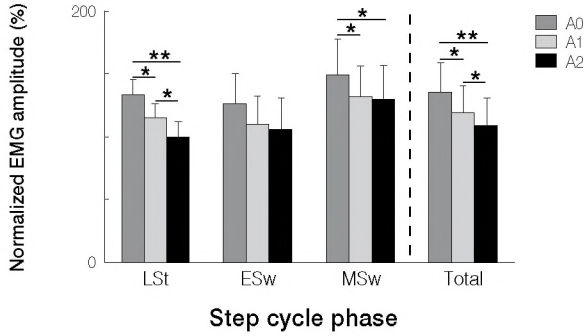


Response amplitude

Figure 6 shows the results of the normalized response amplitudes. Repeated measures MANOVA revealed a main effect of alcohol condition on overall BF response amplitudes ($F_{2,11}$=4.83, p=0.03). Post-hoc analyses yielded a significant effect of alcohol condition on response time in LSt, MSw, and in total (Table 2). A trend for decreasing amplitude with increasing BACs can be noted in all step cycle phases (Figure 6).

Figure 6 Effect of alcohol on normalized EMG amplitudes for the m. biceps femoris

LSt=Late Stance, Esw=Early Swing, MSw=Mid Swing. A0: placebo, A1: first alcohol, A2: second alcohol. (*p<0.05)



To rule out the possible effect of background activity on amplitude, the background activity was analyzed as well. The normalized background activity did not change significantly with increasing BACs ($F_{2,11}$=0.24, p=0.79).

Table 2 Repeated measures MANOVA with within subjects contrast for BF response amplitudes

A0 = placebo, A1 = first alcohol, A2 = second alcohol, LSt = Late Stance, ESw = Early Swing, MSw = Mid Swing, Total = all trials, Diff = difference. Bold numbers indicate significance.

	LSt			ESw			MSw			Total		
	Diff(%)	$F_{1,12}$	*p*	*Diff(%)*	$F_{1,12}$	*p*	*Diff(%)*	$F_{1,12}$	*p*	*Diff(%)*	$F_{1,12}$	*p*
A0 vs A1	18.4	3.5	0.087	15.8	4.6	0.054	17.1	4.7	**0.050**	16.5	9.1	**0.011**
A1 vs A2	14.7	11.2	**0.006**	4.2	2.3	0.158	1.5	2.5	0.142	10.1	9.1	**0.011**
A2 vs A0	33.1	8.3	**0.014**	20	4.7	0.052	18.6	5.7	**0.035**	26.5	10.3	**0.007**

Discussion

The present study investigated the effect of low to moderate levels of alcohol consumption on obstacle avoidance reactions during gait. The results clearly show that even with low BACs (<0.06%), reactions to sudden gait perturbations are seriously affected. After ingestion of 2 alcoholic drinks, obstacles were hit more often, BF response times were delayed and response amplitudes were reduced. These changes were most obvious in situations with little available response time.

This is the first study to investigate the effect of alcohol on responses to sudden gait perturbations (as a relevant task related of falls). Previous studies have concentrated on the effects on posture [16,17]. Low doses usually increased body sway but in some subjects the inverse was seen, indicating that these doses may have an beneficial effect in some cases [17]. However, it is questionable whether these data are actually relevant for falls since falls rarely occur during standing. Locomotion studies seem to be more relevant in this respect. Mallinson et al.[18] found that it may be possible to detect subtle dynamic imbalance induced by alcohol ingestion (89 ml of 40% alcohol) during tandem walking with eyes closed. In the present study participants had to walk on a treadmill with eyes open after consuming an average of 125 ml of 40% alcohol. Because the background activity was not significantly different between the alcohol conditions,

and the obstacle was only released when a regular walking pattern was observed and after at least five unperturbed strides had been taken from the start of the trial, we feel confident that any differences found in the failure rate and any changes in BF activity reflect the effect of the increased BAC.

Earlier research has shown that many falls are primarily due to stumbling and tripping [19]. In order to avoid falls due to hitting an obstacle, one needs to be able to respond adequately to both unseen obstacles causing a stumble [20,21], and to obstacles suddenly appearing in the travel path [6]. The muscle that shows the First major response in all these reactions is the m. biceps femoris [6,15,20,21]. When compared to young adults, both an increase in response latency and a decrease in response amplitudes of this muscle were found in older adults [6,22]. These longer onset latencies and smaller amplitudes were associated with lower success rates [6]. The underlying mechanism for the decreased amplitudes during the stumbling and obstacle avoidance reactions in older adults may involve various age-related physiological changes, both in the CNS (e.g. fewer motoneurons) [23] and in skeletal muscle properties (fewer type II muscle fibers and overall muscle atrophy) [23,24]. In contrast, in the present study the delay and decrease in response are more likely to be due to CNS changes. A possible explanation for the increased failure rate could be that the pathways used in the avoidance reactions have been altered by alcohol consumption. Obstacle avoidance reactions are often very fast; this has led to the proposal that fast supraspinal pathways may be involved that bypass the primary motor cortex [6,25]. These pathways may involve the parietal cortex and/or the cerebellum. For example in studies on cats, Drew [26] showed that the parietal cortex is involved in obstacle avoidance. They also proposed that both a fast directly descending pathway originating from the parietal cortex may exist along with a slower one involving the motor cortex.

Another possible explanation for the impaired obstacle avoidance skills after alcohol consumption lies at the level of neurotransmitters. For example, previous research has shown that the endorphinergic system [27] and GABA (Gamma-Amino Butyric Acid) [28] are intimately involved in the actions of alcohol. The sedative, tranquilizing and/or anaesthetic properties of alcohol have been related to the enhancement of the flow of chlorine ions across neural membranes due to GABA [28]. Yet alcohol does not have this effect on all GABA receptors. Motor incoordination due to ethanol is caused by potentiation of $GABA_A$-associated adenosine A2A receptors in the striatum (caudate nucleus and putamen) [28]. Moreover, it is suggested that alcohol-induced deterioration in motor function

is linked to changes in patterns of brain activity rather than changes in specific brain regions. Specifically, changed activity in the cerebellum as well as in the frontal and parietal cortices are involved in the motor-incoordinating effects of alcohol [29].

Studies on the effects of alcohol on brain activity with leg movements are lacking. However, for arm movements Van Horn et al. [30] found that the human cerebellum and PPC (Posterior Parietal Cortex) are involved in goal-oriented limb movements and that this role is compromised by alcohol. In particular, alcohol may cause a disturbance in the ability of these brain regions to compute appropriate corrective behavioral responses [30]. In this context it is reasonable to suggest that the presently observed deficits in obstacle avoidance skills may be due to the effect of alcohol on information processing in the PPC and the cerebellum. Experiments involving techniques to record brain activity during obstacle avoidance should be performed to test this hypothesis.

Limitations

To limit discomfort to the subjects we used a handheld breath analyzer instead of blood samples. In contrast to blood analysis, these breath analyzers are easy and quick to use, do not require additional hard or software, and are not a burden to the participants. The readings of such portable devices are in good agreement with the results of confirmatory analyses performed by stationary devices (r=0.978) [31]. Furthermore, the correlation with blood analysis is quite high for both the readings of the handheld (r=0.940) as well as the stationary devices(r=0.936) [31].

To the best of our knowledge, the effect of alcohol or other substances on obstacle avoidance during gait has never been studied before in healthy senior individuals. Therefore, it is not possible to make a direct comparison with results from similar studies. However, the obstacle avoidance task used in the present study has proven to be sensitive enough to detect significant agerelated deficits [32]. A possible limitation is the relatively small sample size. However, in this type of motor control studies it is quite usual to have similar group sizes (because of the extensive data analysis involved). Furthermore, even with the small number the study yielded unequivocal outcomes. Hence, a larger sample size will mostly accentuate the significance of the present results.

Conclusions

In conclusion, the present results clearly show that alcohol levels, considered to be safe for driving, seriously hamper the ability to successfully avoid sudden obstacles in the travel path. It is suggested that many of the alcohol-related falls are the result of the disruptive effects of alcohol on the online corrections of the ongoing gait pattern when walking under challenging conditions. In general the use of alcohol is primarily seen as a risk factor for driving [1,33]. However, Kool et al. [2] estimated that approximately 20% of unintentional falls at home in a working-aged population may be attributable to the consumption of two or more standard alcoholic drinks in the preceding 6 h. Moreover, accidents can also occur while walking, particularly under challenging conditions such as when negotiating suddenly appearing obstacles. The present data show that the required skills for obstacle avoidance frequently fail even after consumption of a low dose of alcohol.

References

1. Ogden EJ, Moskowitz H: **Effects of alcohol and other drugs on driver performance.** *Traffic Inj Prev* 2004, **5:**185-198.
2. Kool B, Ameratunga S, Robinson E, Crengle S, Jackson R: **The contribution of alcohol to falls at home among working-aged adults.** *Alcohol* 2008, **42:**383-388.
3. Kannus P, Parkkari J, Koskinen S, Niemi S, Palvanen M, Jarvinen M, Vuori I: **Fall-induced injuries and deaths among older adults.** *JAMA* 1999, **281:**1895-1899.
4. Weerdesteyn V, Nienhuis B, Duysens J: **Advancing age progressively affects obstacle avoidance skills in the elderly.** *Hum Mov Sci* 2005, **24:**865-880.
5. Hofstad CJ, Weerdesteyn V, van der Linden H, Nienhuis B, Geurts AC, Duysens J: **Evidence for bilaterally delayed and decreased obstacle avoidance responses while walking with a lower limb prosthesis.** *Clin Neurophysiol* 2009, **120:**1009-1015.
6. Weerdesteyn V, Nienhuis B, Geurts AC, Duysens J: **Age-related deficits in early response characteristics of obstacle avoidance under time pressure.** *J Gerontol A Biol Sci Med Sci* 2007, **62:**1042-1047.
7. Drew T, Jiang W, Kably B, Lavoie S: **Role of the motor cortex in the control of visually triggered gait modifications.** *Can J Physiol Pharmacol* 1996, **74:**426-442.
8. Drew T, Andujar JE, Lajoie K, Yakovenko S: **Cortical mechanisms involved in visuomotor coordination during precision walking.** *Brain Res Rev* 2008, **57:**199-211.
9. Tiihonen J, Kuikka J, Hakola P, Paanila J, Airaksinen J, Eronen M, Hallikainen T: **Acute ethanol-induced changes in cerebral blood flow.** *Am J Psychiatry* 1994, **151:**1505-1508.
10. Volkow ND, Mullani N, Gould L, Adler SS, Guynn RW, Overall JE, Dewey S: **Effects of acute alcohol intoxication on cerebral blood flow measured with PET.** *Psychiatry Res* 1988, **24:**201-209.
11. Volkow ND, Ma Y, Zhu W, Fowler JS, Li J, Rao M, Mueller K, Pradhan K, Wong C, Wang GJ: **Moderate doses of alcohol disrupt the functional organization of the human brain.** *Psychiatry Res* 2008, **162:**205-213.
12. Chen HC, Ashton-Miller JA, Alexander NB, Schultz AB: **Effects of age and available response time on ability to step over an obstacle.** *J Gerontol* 1994, **49:**M227-M233.
13. Hermens HJ, Freriks B, Merletti R, Hägg GG, Stegeman D, Blok J, Rau G, Disselhorst-Klug C: *SENIAM 8: European Recommendations for Surface ElectroMyoGraphy.* Enschede, The Netherlands: Roessingh Research and Development b.v.; 1999.
14. Widmark EMP: *Principles and Applications of Medicolegal Alcohol Determination.* Davis, CA: Biomedical Publications; 1981.
15. Queralt A, Weerdesteyn V, van Duijnhoven HJ, Castellote JM, Valls-Sole J, Duysens J: **The effects of an auditory startle on obstacle avoidance during walking.** *J Physiol* 2008, **586:**4453-4463.
16. Boonstra TW, Roerdink M, Daffertshofer A, van VB, van WG, Beek PJ: **Low-alcohol doses reduce common 10- to 15-Hz input to bilateral leg muscles during quiet standing.** *J Neurophysiol* 2008, **100:**2158-2164.
17. Nieschalk M, Ortmann C, West A, Schmal F, Stoll W, Fechner G: **Effects of alcohol on body-sway patterns in human subjects.** *Int J Legal Med* 1999, **112:**253-260.
18. Mallinson AI, Longridge NS, Morley RE: **Evaluation of the effects of ethanol on static and dynamic gait.** *J Otolaryngol Head Neck Surg* 2008, **37:**856-859.
19. Berg WP, Alessio HM, Mills EM, Tong C: **Circumstances and consequences of falls in independent community-dwelling older adults.** *Age Ageing* 1997, **26:**261-268.
20. Pijnappels M, Bobbert MF, van Dieen JH: **Control of support limb muscles in recovery after tripping in young and older subjects.** *Exp Brain Res* 2005, **160:**326-333.
21. Schillings AM, van Wezel BM, Mulder T, Duysens J: **Muscular responses and movement strategies during stumbling over obstacles.** *J Neurophysiol* 2000, **83:**2093-2102.
22. Schillings AM, Mulder T, Duysens J: **Stumbling over obstacles in older adults compared to young adults.** *J Neurophysiol* 2005, **94:**1158-1168.
23. Mynark RG, Koceja D.M.: **Effects of age on the spinal stretch reflex.** *J Appl Biomech* 2001, **17:**188-203.
24. Porter MM, Vandervoort AA, Lexell J: **Aging of human muscle: structure, function and adaptability.** *Scand J Med Sci Sports* 1995, **5:**129-142.

25. Reynolds RF, Day BL: **Visual guidance of the human foot during a step.** *J Physiol* 2005, **569:**677-684.
26. Drew T, Kalaska J, Krouchev N: **Muscle synergies during locomotion in the cat: a model for motor cortex control.** *J Physiol* 2008, **586:**1239-1245.
27. Blum K, Briggs AH, Trachtenberg MC: **Ethanol ingestive behavior as a function of central neurotransmission.** *Experientia* 1989, **45:**444-452.
28. Meng ZH, Anwer J, Dar MS: **The striatal adenosinergic modulation of ethanol-induced motor incoordination in rats: possible role of chloride flux.** *Brain Res* 1997, **776:**235-245.
29. Zhu W, Volkow ND, Ma Y, Fowler JS, Wang GJ: **Relationship between ethanol-induced changes in brain regional metabolism and its motor, behavioural and cognitive effects.** *Alcohol Alcohol* 2004, **39:**53-58.
30. Van Horn JD, Yanos M, Schmitt PJ, Grafton ST: **Alcohol-induced suppression of BOLD activity during goal-directed visuomotor performance.** *Neuroimage* 2006, **31:**1209-1221.
31. Zuba D: **Accuracy and reliability of breath alcohol testing by handheld electrochemical analysers.** *Forensic Sci Int* 2008, **178:**e29-e33.
32. Weerdesteyn V, Schillings AM, van Galen GP, Duysens J: **Distraction affects the performance of obstacle avoidance during walking.** *J Mot Behav* 2003, **35:**53-63.
33. Glucksman E: **Alcohol and accidents.** *Br Med Bull* 1994, **50:**76-84.

3

Dual task effects for asymmetric stepping on a split-belt treadmill

McFadyen BJ, Hegeman J, Duysens J: **Dual task effects for asymmetric stepping on a split-belt treadmill.** *Gait Posture* 2009, **30:** 340-344.

Abstract

Bilaterally asymmetric stepping during walking is common to a number of pathological gaits (e.g., hemiplegia, limping). In the present work, the attention level of asymmetric stepping was studied by having subjects walk on a split-belt treadmill with symmetric (2 km/hr) and asymmetric (2 vs 4 and 2 vs 6 km/hr) belt speeds both with and without a dual auditory Stroop task. There was no significant change in response reaction times across walking conditions or between walking and standing. The proportion of stance phase was unchanged by the dual task during symmetric walking. Stance phase proportions, however, significantly increased during dual tasking for the limb on the faster belt for both asymmetric conditions, while they decreased for the limb on the slower belt for the most asymmetric condition. There were also small modifications to double support proportions and a main effect of dual tasking to double support proportion variability. Observed dual task changes showed interference by the cognitive task with asymmetric gait performance, suggesting that asymmetric stepping, such as seen in limping gaits, requires more attention than symmetric walking. Such attention may, in part, be due to the dynamic balance required in asymmetric limb loading and unloading.

Introduction

A number of pathological gaits involve bilaterally asymmetric stepping. Different methods, such as using a rotating treadmill [1] or a split-belt treadmill [2], have been used to study asymmetric walking. The split-belt paradigm provides a controlled means to simulate limping-like, straight-ahead gait at controlled speeds. Research using such protocols has shown that young adults can adapt to different split-belt speed asymmetries accommodating new inter-limb coordination patterns [2,3]. There also appear to be different control mechanisms in asymmetric gait as compared to symmetric gait in relation to muscular coordination at the ankle joint. These different mechanisms are due to a change in interaction of the timing and coordination for the unloading of one limb in late stance with the loading of the contralateral limb in early stance [2,4,5]. In particular, based on the analysis of ground reaction forces and ankle muscle activity in limping patients, De Visser et al. [6] showed that automated phase switching does not rely primarily on ipsilateral mechanisms. Instead, the onset of ipsilateral swing is linked to the moment of load acceptance by the contralateral leg.

For their part, Reisman et al. [3] interpreted observed adaptations to different split-belt speeds as the storage of new inter-limb coordination patterns. These authors also suggested an independence of control of each limb, as well as independence between inter- and intra-limb coordination. Yang et al. [7], in looking at infant stepping on a split-belt treadmill, also concluded that each limb was under the control of separate pattern generators, but still coupled together.

Based on these observations one would predict that the coupling between the legs during limping is relatively automated but it still may require more attention than symmetric gait. However, this has never been tested. It has been established through the use of dual task protocols that normal, symmetric walking itself requires a certain level of attention [c.f. 8], especially in the elderly [e.g., 9,10] and in patients who have recovered from various types of leg surgery [e.g., 11]. It is also known that the attention level of walking is increased at speeds other than natural speeds in both healthy [12] and pathological [11,13] walking, as well as when healthy subjects are forced to walk in a manner that is not habitual, such as at high speeds when a running gait would normally be used [14].

Asymmetric walking involves speeds and gait behaviour neither of which is habitual, although still performed in a stereotypic and even automatic manner. Understanding the attention level of asymmetric walking patterns will not only expand the study of the attention demands to walking under different conditions,

but also provide information to better understand the demands of a behaviour common to many pathological gaits. The goal of this work, therefore, was to study whether asymmetric walking (such as would be found during limping) demands greater attention than symmetric walking. It was hypothesized that despite its automatic nature, asymmetric walking, requiring different contralateral timing and dynamic equilibrium control, will demand more attention expressed by interference in the performance of both the simultaneous cognitive and gait tasks as compared to their single task performances.

Methods

Participants

Eleven healthy, young (26.2±3.8 years, 5 male) subjects were recruited from the Nijmegen University Medical Centre community. Based on self-reporting, subjects had no current neurological or musculoskeletal problems and had normal or corrected-to normal vision. All participants provided written consent according to the Declaration of Helsinki.

Equipment and procedure

Subjects walked with each foot on separate, individually controlled treadmills (ForceLink BV, The Netherlands; Figure 1). All subjects wore a harness that did not impede walking and would only be engaged in the case of loss of balance. Belt speeds for each treadmill could be the same (symmetric condition) or different (asymmetric condition). Force transducers placed under the corners of each treadmill closest to subject's feet were used to provide stance and stride times and to subsequently calculate stance phase and double support phases as a proportion of respective left and right stride times. Subjects also wore headphones that delivered the simultaneous auditory Stroop task consisting of a high or low pitched voice saying the words "high" or "low" in Dutch. Subjects were required to indicate the pitch of the voice and to ignore the word said. Twenty-one voice stimuli were given during the dual task conditions at an average rate of 1.5 s between stimuli onsets with approximately equal incongruent (voice pitch and word do not match) and congruent (voice pitch and word match) Stroop stimuli (10:11). Stimuli, voice and force transducer data were all recorded at 1000 Hz.

Figure 1 Split-belt set-up with fixed speed on the left side and varying speeds on the right side. Small black arrow heads indicate positions of force transducers used for stride timing

Three belt speed conditions were studied. These included symmetric speeds at 2 km/h and two asymmetric speeds with the left limb at 2 km/h and the right limb at either 4 km/h or 6 km/h. Subjects initially stood on the two static treadmills that were then brought to 2 km/h together. For the asymmetric conditions, the right treadmill was then further increased to the targeted higher speed. After establishing the targeted speeds for each side, a minimum of 15 further strides were given to accommodate to the speeds. Verbal confirmation of the subject being comfortable with the speeds was attained before collecting data. Data were first collected for the walking tasks only at different belt speeds from symmetric to progressively asymmetric. Next, subjects were introduced to the auditory Stroop task and performed it while standing with the treadmills off, first in order to confirm their understanding of the task and then to collect the single task Stroop condition. Follow this standing recording, subjects were then required to walk at the different speeds with the dual task. The instructions for the walking task were to walk as stable as possible while looking at a target (a cross on the

wall) straight ahead. The instruction for the Stroop task was to indicate as quickly as possible whether the voice pitch was high or low. Thus, both walking and cognitive tasks were prioritized. Speed conditions were counterbalanced across subjects during the dual task conditions to minimize conditioned effects of order from the first block of single task data collection. Following each walking period for a given speed condition, the right belt speed was decreased to match the left one and then subjects walked until they felt comfortable (i.e., no after-effects), after which the two treadmills were then slowed to a stop.

Data analysis

Response reaction times (RRTs) were calculated using custom software programmed in Matlab 7.2 (The Mathworks Inc., US) to detect the difference between the start of the Stroop stimuli signal and the start of the response voice signal. Gait temporal data derived from the force transducers were used to calculate the stride time, stance time as a proportion of stride for each limb and double support time following heel contact for each limb. For each condition, temporal data were averaged over a minimum of 20 strides, and corresponded to the period of verbal response for the dual task conditions. RRTs were averaged for all 21 responses for each dual task condition. Intra-subject variability of this data was also calculated from each subject's standard deviation across the number of strides used for the condition.

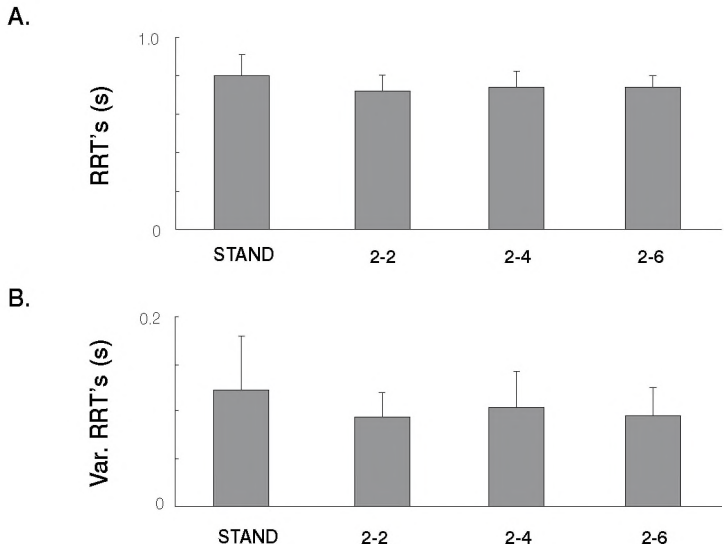
Statistical analysis

A three-way generalised repeated measures ANOVA (belt speed by dual task by limb side) was used to evaluate main and interaction effects for gait variables. Since RRTs were only collected for dual tasks and not related to limb, a one-way ANOVA was used to evaluate main effects for RRT and intra-subject variability across belt speed conditions (including standing). Post hoc Student's t-tests were performed for significant ($p \leq 0.05$) main effects.

Results

Response reaction times tended to be slightly faster during gait as compared to standing (Figure 2A), but there were no significant main effects across conditions. Intra-subject variability in these RRTs followed the same trend as the reaction time amplitudes (Figure 2B), but again with no main effects found.

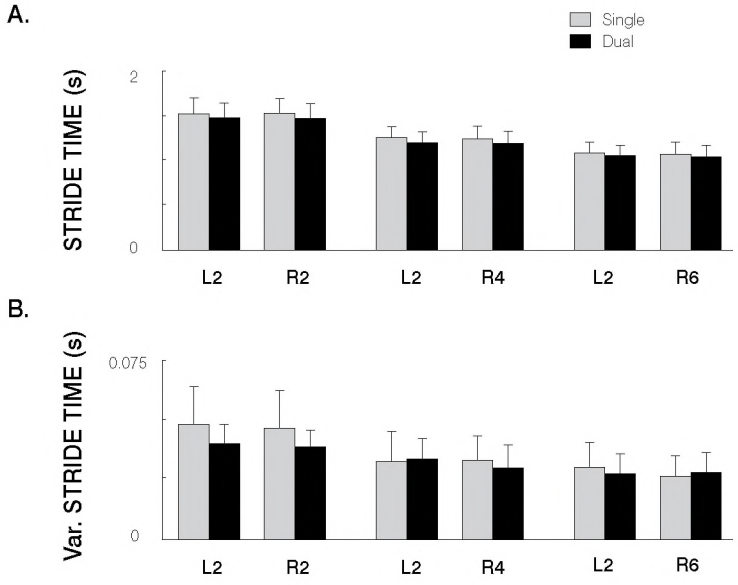
Figure 2 **A**. Response reaction times (RRTs) and **B**. the intra-subject variability in response to the Stroop task during standing and different walking conditions. Error bars indicate standard deviations



There was a main effect of belt speeds ($p<0.001$) on stride time corresponding to equal bilateral decreases with increasing belt asymmetry (Figure 3A). There were, however, no dual task or limb effects and no interactions between factors. As has been shown in the past [2], the left limb, even though maintaining the same speed, also decreased its time in a coupled manner with the right limb. Intra-subject variability in stride time resulted in a main effect for belt speed ($p<0.001$), again decreasing with increased asymmetry and a small effect for limb ($p=0.045$), although no post hoc differences for either variable were found (Figure 3B). Dual task effects again were not significant. There were no interactions between conditions.

Despite the maintenance of stride timing bilaterally, there were main effects for belt speed ($p<0.001$) and limb ($p<0.001$) on the proportion of stance time such that stance proportion was longer on the slow side and shorter on the fast side for asymmetric conditions (Figure 4A). There was no dual task main effect, but there were significant interactions between factors of dual task and belt speed

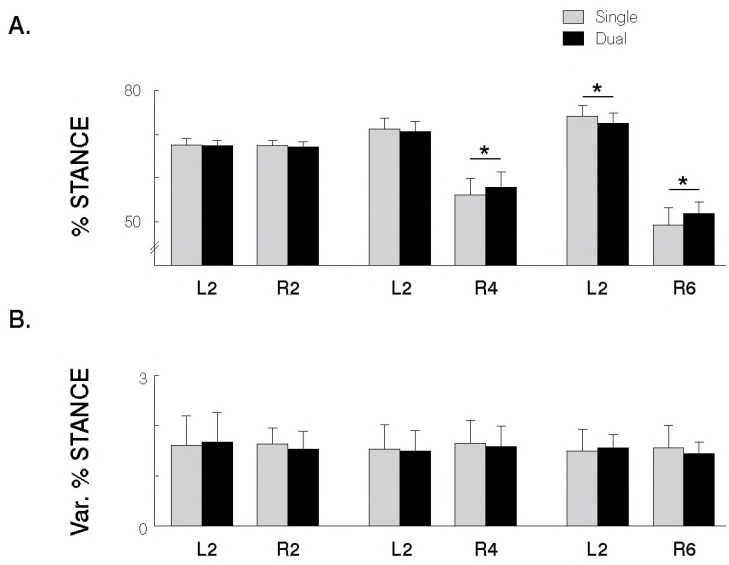
Figure 3 **A**. Stride times and **B**. their intra-subject variability for the left [L] and right [R] limbs during single (grey bars) and dual (black bars) tasks over the different walking conditions. Error bars indicate standard deviations



(p=0.014), dual task and limb (p=0.002), belt speed and limb (p<0.001), as well as between all three factors (p=0.023). Further analyses showed that the dual task did not affect stance phase proportion in the symmetric condition, but this variable was significantly different for dual versus single tasking for asymmetric conditions being increased for the faster limb at both the 2–4 and 2–6 conditions (p=0.004 and p=0.003 respectively) and decreased for the slower limb in the 2–6 condition (p=0.004). This difference in the slower limb did not show significance for the 2–4 condition. The intra-subject variability remained the same across conditions and limbs (Figure 4B).

When the double support phase proportions were analysed (Figure 5A), main effects of belt speed (decreasing with split-belt conditions; p<0.001) and limb (always slightly higher for the right limb; p=0.001) were found, but there were no main dual tasking effects. There were significant interactions, however, between

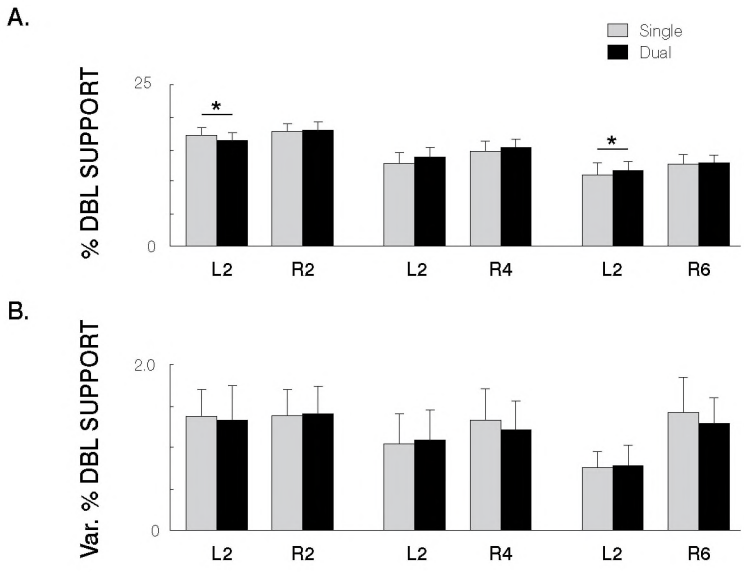
Figure 4 **A**. Stance phase periods as a proportion of stride and **B**. their intra-subject variability for the left [L] and right [R] limbs during single (grey bars) and dual (black bars) tasks over the different walking conditions. Error bars indicate standard deviations. Asterisks indicate differences between dual and single tasks for a given treadmill condition ($p \leq 0.05$)



speed and dual tasking conditions ($p=0.009$) and between all three factors ($p=0.015$). Further analyses showed that only the left limb during symmetric gait and during the 2–6 condition had significant differences due to dual tasking.

Finally, intra-subject variability in double support proportions (Figure 5B) showed main effects for belt speed ($p=0.005$), for dual tasking ($p=0.032$) and for limb side ($p<0.001$). In addition, there was a significant interaction between belt speed side and limb ($p=0.008$). Specifically, variability in the slow (left) limb decreased in the asymmetric conditions and dual tasking caused the faster right limb to be less variable in the asymmetric conditions than during single task walking. Further analyses, however, failed to show any significant differences between factors.

Figure 5 **A**. Double support phase periods as a proportion of stride and **B**. their intra-subject variability for the left [L] and right [R] limbs during single (grey bars) and dual (black bars) tasks over the different walking conditions. Error bars indicate standard deviations. Asterisks indicate differences between dual and single tasks for a given treadmill condition ($p \leq 0.05$).



Discussion

A split-belt treadmill protocol was used to study the attention levels required for asymmetric stepping. Response reaction times to the auditory Stroop task suggest little modification to the cognitive task, but gait data showed significant and clear dual task effects to relative timing of the bilateral support phases. Effects on the variability in the dependent variables within subjects were minimal. The lack of effects on the cognitive task (RRTs), specifically from standing to walking, was contrary to what was expected for the more challenging asymmetric gait. It is possible that the cognitive task we chose was simple enough to perform consistently across conditions, but still interfered with gait timing. The tendency

for higher and more variable RRTs during standing may indicate some learning although these were not significant. There is precedent for such a finding for symmetric treadmill walking [15]. Future work might include re-testing the standing cognitive condition at the end of walking. However, noted changes in gait timing variables between single and dual task walking indicate that both tasks cannot be executed simultaneously without some interference in performance.

As already established in early [2] and more recent [3] studies, stride timing was bilaterally equal for all conditions, although decreasing when one limb was required to speed up. This is simply the result of the need for maintaining stable gait and can be shown for other asymmetrical stepping situations such as curved path walking [16]. Given that the simultaneous Stroop task of the present study did not affect stride timing or its variability, these aspects of bilateral timing would appear to be automatic features of gait, particularly on the treadmill.

The fact that subjects spent more of their stride in stance on the slow limb and less on the fast limb during asymmetric gait seems logical given the speeds with which the respective belts would transport the limb under the body. This would also explain the double support proportions that were slightly greater on the fast side (as slow limb stays longer) and slightly less on the slow side (as the fast limb picks up sooner). The maintenance of equal stride timing discussed above would then reciprocally result in a swing proportion that is shorter on the slow side and longer on the fast side. These differences in relative phase timings are the very visual quality that we identify with limping. However, what is interesting is that the stance phase proportion on the fast limb with increasing asymmetric speeds was increased during dual tasking, supporting the hypothesis for interference by the cognitive task on gait in such a situation. This interference shows that, although stride timing may be automatic in nature, asymmetric gait performance requires some attention. Specifically, it suggests that relative timing of the stance and swing phases, and perhaps particularly support on the faster side, require attention during asymmetric walking.

Part of the reason for the greater need in attention in asymmetric stepping may be the increased dynamic balance requirements in asymmetric loading and unloading of the limbs. As has been previously shown, walking under split-belt conditions elicits different control mechanisms as compared to symmetric gait, in particular in relation to the interaction of the timing and coordination for the transfer of loading between limbs [2,4,5]. Also, it has been suggested that inter-limb coupling is re-organized and even relearned during split-belt treadmill walking [3]. With the present data, the fact that the right and left double support

times were similar in the split-belt conditions supports that subjects had relearned this pattern [see 3] and further that this relearned pattern is fairly robust. Dual tasking was able to interfere with the adjusted pattern somewhat but nevertheless these changes were relatively modest, indicating that the underlying coordination is still fairly automated. This is consistent with it being dependent primarily on subcortical structures such as the cerebellum.

The observed changes in stance phase percentages were not particularly large (in the order of about 2 percent between asymmetric and symmetric gaits). Changes in double support phases were also small. Yet, as seen from the variability data, relative stance phase timing is very consistent and, therefore, small changes are significant. The fact that intra-subject variability was consistent even though relative stance timing was changed during dual tasking shows the robust nature of the temporal aspect of this stepping behaviour by the locomotor control system. In particular, these changes in relative stance phase timing during dual tasking with low and consistent variability also suggest that this behaviour is probably directly due to a decision to augment stability with a greater stance phase, rather than an inability to maintain it.

Why would asymmetric, limping-like, stepping require more attention for control of support phase relative timing than symmetric stepping? A few studies have considered the information processing involved at cortical and subcortical levels for split-belt walking. Duysens et al. [17], looking at specific mechanisms of muscle control over such loading coordination using split-belt walking, have shown cortical involvement over the complex sensori-motor integration of ankle muscles. In addition, two papers looking at the ability to adapt to split-belt asymmetric speeds in persons with stroke [18] and with cerebellar deficits [19] have suggested that inter-limb coordination adaptation is mediated specifically by cerebellar influence through brainstem circuits. In the intact human, such as for the present study, the small intra-subject variability for all measures, even during dual tasking, shows that even the more complex form of locomotion induced by the split-belt treadmill is relatively automated. This level of automation may be in large part due to a dominant role by subcortical structures such as the cerebellum. However, the present results also show that such coordination, even when adaptation is achieved, still demands some attention in support phase relative timing, possibly related to issues of dynamic equilibrium.

Some caution must be taken in interpreting the results for over ground walking. Walking on a split-belt treadmill is very controlled while over ground limping would most likely be more variable in its timing. In addition, there can be many reasons

for a limping gait. Usually, however, limping is related to some discomfort and a need to load the limbs differently in order to reduce or avoid pain whether it be from an external perturbation (e.g., foreign object in one's shoe) or, more commonly, an internal source (e.g., tissue strain leading to pain such as arthritis or myofacial pain). How such discomfort, and particularly pain itself, would affect attention is important and cannot be addressed with the present work. Presumably, pain would by itself affect the attention capacity of the person [20]. Furthermore, it is likely that the "learning" of asymmetrical gait requires more attention in the short term, but less in the long term as has been shown for the case of podokinetics (i.e., walking on a disc; [1]).

Finally, we cannot say if dual task effects might have been more prominent had the subjects walked without a harness. Even though the harness did not provide any mechanical influence and no subject required it at any time during the study, it is possible that it provided more confidence in dynamic balance and, therefore, less attention required with than without it.

Conclusions

In conclusion, although asymmetric stepping maintains some automaticity in stride timing, it also appears to require some attention for dynamic equilibrium resulting in a strategy of prolonging the proportion of time put on the shorter stance phase. This strategy for increased dynamic stability may be mediated by supraspinal control as discussed previously in the literature. Continuing from this controlled experiment, further research should consider overground pathological limping gaits.

References

1. Earhart GM, Jones GM, Horak FB, Block EW, Weber KD, Fletcher WA: **Podokinetic after-rotation following unilateral and bilateral podokinetic stimulation.** *J Neurophysiol* 2002, **87:** 1138-1141.
2. Dietz V, Zijlstra W, Duysens J: **Human neuronal interlimb coordination during split-belt locomotion.** *Exp Brain Res* 1994, **101:** 513-520.
3. Reisman DS, Block HJ, Bastian AJ: **Interlimb coordination during locomotion: what can be adapted and stored?** *J Neurophysiol* 2005, **94:** 2403-2415.
4. Duysens J, Clarac F, Cruse H: **Load-regulating mechanisms in gait and posture: comparative aspects.** *Physiol Rev* 2000, **80:** 83-133.
5. Prokop T, Berger W, Zijlstra W, Dietz V: **Adaptational and learning processes during human split-belt locomotion: interaction between central mechanisms and afferent input.** *Exp Brain Res* 1995, **106:** 449-456.
6. De Visser E, Veth RP, Schreuder HW, Duysens J: **Altered phase-transitions in tibialis anterior and medial gastrocnemius during walking after limbsaving surgery.** *Clin Neurophysiol* 2005, **116:** 2741-2747.
7. Yang JF, Lamont EV, Pang MY: **Split-belt treadmill stepping in infants suggests autonomous pattern generators for the left and right leg in humans.** *J Neurosci* 2005, **25:** 6869-6876.
8. Woollacott M, Shumway-Cook A: **Attention and the control of posture and gait: a review of an emerging area of research.** *Gait Posture* 2002, **16:** 1-14.
9. Lundin-Olsson L, Nyberg L, Gustafson Y: **"Stops walking when talking" as a predictor of falls in elderly people.** *Lancet* 1997, **349:** 617.
10. Faulkner KA, Redfern MS, Cauley JA, Landsittel DP, Studenski SA, Rosano C *et al.*: **Multitasking: association between poorer performance and a history of recurrent falls.** *J Am Geriatr Soc* 2007, **55:** 570-576.
11. Bodde EW, De Visser E, Duysens JE, Hartman EH: **Donor-site morbidity after free vascularized autogenous fibular transfer: subjective and quantitative analyses.** *Plast Reconstr Surg* 2003, **111:** 2237-2242.
12. Kurosawa K: **Effects of various walking speeds on probe reaction time during treadmill walking.** *Percept Mot Skills* 1994, **78:** 768-770.
13. De Visser E, Pauwels J, Duysens JE, Mulder T, Veth RP: **Gait adaptations during walking under visual and cognitive constraints: a study of patients recovering from limb-saving surgery of the lower limb.** *Am J Phys Med Rehabil* 1998, **77:** 503-509.
14. Abernethy B, Hanna A, Plooy A: **The attentional demands of preferred and non-preferred gait patterns.** *Gait Posture* 2002, **15:** 256-265.
15. Fraser SA, Li KZ, DeMont RG, Penhune VB: **Effects of balance status and age on muscle activation while walking under divided attention.** *J Gerontol B Psychol Sci Soc Sci* 2007, **62:** 171-178.
16. Courtine G, Schieppati M: **Human walking along a curved path. II. Gait features and EMG patterns.** *Eur J Neurosci* 2003, **18:** 191-205.
17. Duysens J, Bastiaanse CM, Smits-Engelsman BC, Dietz V: **Gait acts as a gate for reflexes from the foot.** *Can J Physiol Pharmacol* 2004, **82:** 715-722.
18. Reisman DS, Wityk R, Silver K, Bastian AJ: **Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke.** *Brain* 2007, **130:** 1861-1872.
19. Morton SM, Bastian AJ: **Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking.** *J Neurosci* 2006, **26:** 9107-9116.
20. Lamoth CJ, Stins JF, Pont M, Kerckhoff F, Beek PJ: **Effects of attention on the control of locomotion in individuals with chronic low back pain.** *J Neuroeng Rehabil* 2008, **5:** 13.

4

Dual-tasking interferes with obstacle avoidance reactions in healthy seniors

Hegeman J, Weerdesteyn V, van den Bemt BJ, Nienhuis B, van Limbeek J, Duysens J: **Dual-tasking interferes with obstacle avoidance reactions in healthy seniors.** *Submitted*

Abstract

Dual-tasking can lead to falls, as does a deterioration of obstacle avoidance skills. Hence, it is expected that a combination of both would be even more detrimental, especially when obstacles have to be avoided under time pressure. Previous work confirmed this expectation, however, due to several limitations in the design of previous studies it is yet too early to draw any definitive conclusions on the allocation of attentional resources in obstacle avoidance under dual-task conditions. Therefore, the present study used a primary and secondary task that are both attentionally demanding, with the instruction to perform as well as possible on both tasks. Nineteen healthy senior individuals (60±4.7years, 8 female) performed an obstacle avoidance task on a treadmill while walking at 3km/h as a single task and combined with an auditory Stroop task. Sensitive outcome parameters, m. biceps femoris (BF) response times, obstacle avoidance failure rates and composite scores ((100xaccuracy)/verbal response time), were used to evaluate the data. Increased obstacle avoidance failure rates (3%, $p=0.03$) and delayed BF response times (21ms, $p<0.001$) were found under dual-task conditions. Composite scores were reduced during ($p<0.001$) and just after obstacle crossing ($p=0.003$). In conclusion, dual-tasking while avoiding obstacles under time pressure affects the motor as well as the cognitive task when subjects are instructed to keep up their performance on both. This adds to the evidence indicating an increased risk of tripping or falling when attention is divided during walking in the presence of unexpected obstacles.

Introduction

Poor performance levels on both dual-task walking and obstacle avoidance associate with an increased risk of falling [1,2]. A combination of these tasks, as a common but challenging activity of daily living, is expected to be even more informative with respect to the risk of falling. Several researchers assessed obstacle avoidance combined with a cognitive secondary task and usually found effects of dual-tasking on the primary motor task, even in young and healthy populations [3-9]. Detrimental effects on the secondary task were reported less frequently [10,11], which may suggest that the secondary task is generally prioritized ('posture second strategy'). However, due to several limitations in the design of previous studies it is yet too early to draw any definitive conclusions on the allocation of attentional resources in obstacle avoidance under dual-task conditions.

First, in most dual-task studies on obstacle avoidance participants are not given explicit instructions regarding which task to prioritize, or these instructions are not reported in the paper. This leaves the question whether the detrimental effects on the motor tasks truly reflect a 'posture second' strategy or are due to an implicit assumption of participants that they should keep up performance on the secondary task.

A second limitation is that most of the studies applied an obstacle avoidance task that did not require continuous allocation of attention (i.e. avoiding a stationary obstacle), thereby allowing participants to switch attention between tasks. Furthermore, the studies often evaluated the effects of dual-tasking using rather crude outcomes (e.g. gait velocity or number of errors on the secondary task). Although informative, such paradigms may not be sufficiently sensitive to reveal the full image of dual-task interference. One exception to this is the study of Chen et al. [3]. They used an obstacle avoidance task that required participants to adjust their gait pattern within one step to succeed. This task was combined with and affected by a secondary visual reaction time task. Both tasks, however, relied on visual information and the detrimental effects of the combination of these tasks may also be due to gaze shifts from the obstacle to the visual secondary task stimulus and vice versa. Although such task combinations do simulate a situation commonly encountered during activities of daily living, they probably do not reflect the effects of exceeding the limits of attentional capacity. Therefore, Weerdesteyn et al. [7] used a secondary task that involved another sensory modality (i.e. an auditory Stroop task [12]) in combination with a

time-critical obstacle avoidance task, but they did not evaluate secondary task performance in great detail. Siu et al. combined obstacle avoidance during overground walking with an auditory Stroop task as well [6,11]. They demonstrated that both spatiotemporal gait parameters and verbal response times remained unaffected under dual-task conditions in young adults [11]. In older adults, though, gait velocity decreased and stride length increased when stepping over the obstacle in parallel with increased error rates on the Stroop task [6]. However, the obstacle avoidance task used did not require continuous attention. Hence, it seems possible that the full image of dual-task interference was not revealed by these studies.

Considering the above mentioned limitations, we studied dual-task interference during obstacle avoidance (1) using a primary and secondary task that both require continuous attention for optimal performance, (2) with the explicit instruction to perform as well as possible on both tasks, (3) using outcome parameters that are highly sensitive to identify even subtle effects on either one of the tasks. It was expected that simultaneous performance of a time-critical obstacle avoidance task and a secondary cognitive task would affect performance on both tasks.

Methods

Participants

Nineteen healthy senior individuals (60±4.7years, 8 female) volunteered to participate in this experiment. Inclusion criterion was age between 50-70 years. Subjects were excluded if they suffered from hearing problems, serious neurological, orthopaedic or cognitive impairments, had poor knowledge of Dutch, or used medication that affected the locomotor system. All participants provided written informed consent in accordance with the Declaration of Helsinki. The regional ethics committee of Arnhem and Nijmegen approved this study.

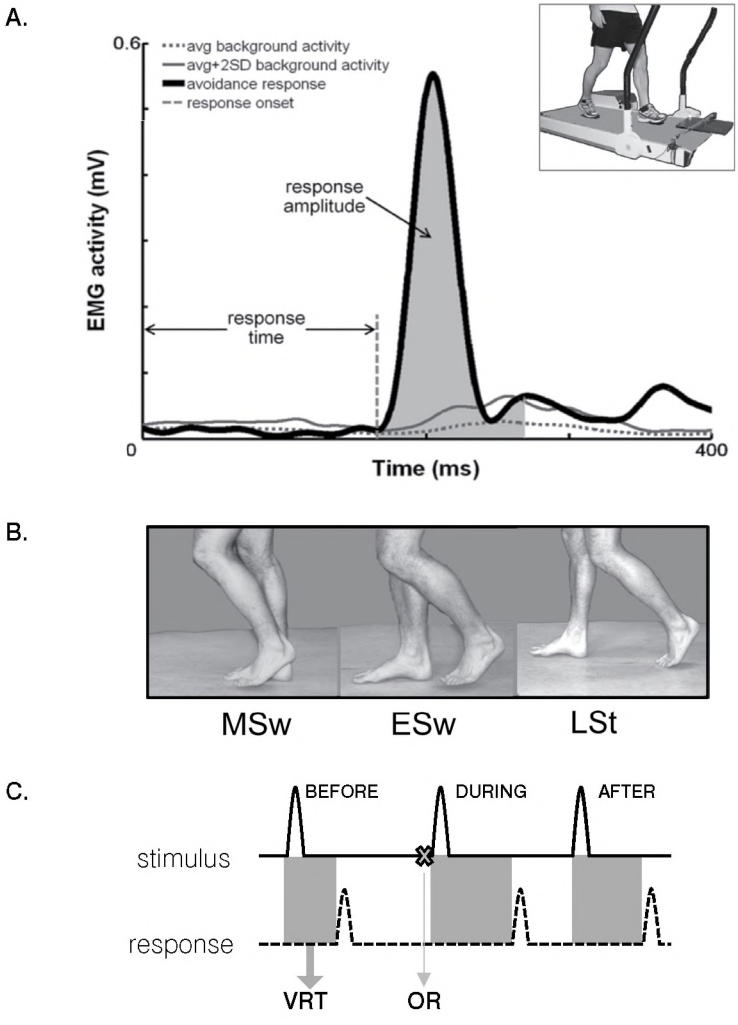
Experimental procedures

Obstacle avoidance task

The participants had to avoid obstacles while walking on a treadmill (ENRAF Nonius, Type EN-tred Reha) at a fixed velocity of 3 km/hr (Figure 1A, inset), wearing their own comfortable low-heeled shoes. A wooden obstacle (measuring 40x30x1.5cm) with an embedded piece of iron was held by an electromagnet just

Figure 1 Methods

A. Determination of response of the m. biceps femoris (BF). Response time was defined as the time between obstacle release (at Time=0) and the instant where the BF activity exceeded the activity of the control stride + 2SD. Inset: experimental setup. **B**. Step cycle phases in which the obstacle was released. MSw = Mid Swing, ESw = Early Swing, LSt = Late Stance. **C**. Determination of verbal response time (VRT = time between the start of the stimulus and the start of the response) and illustration of the stimulus timings: BEFORE, DURING, and AFTER obstacle crossing. OR = obstacle release



above the treadmill surface. Its release was triggered by the computer. The obstacle was always presented to the left foot at a distance of approximately 10cm from the most anterior position reached by the toes in the swing phase. Marker positions of the obstacle and the heel, ankle and big toe of both feet were recorded by an 8-camera 3-D motion analysis system (Vicon®, Oxford Metrics, London, UK) at a sample rate of 100Hz and were processed in real time to determine the timing of obstacle release related to gait phase. Before the obstacle was released stride regularity (a maximum difference of 50ms between two consecutive strides) was needed and at least five unperturbed strides had to be completed. The obstacles were released in three different phases of the step cycle (late stance (*LSt,*45-60% of the step cycle), early swing (*ESw,* 60-70%) or mid swing (*MSw,*70-85%)) to create different difficulty levels as time pressure increased with later obstacle presentation (Figure 1B).

The participants were instructed to look at the obstacle, and step straight over it after its release. Any contact of the left foot with the obstacle or stepping to the side of it was defined as a failure. Surface electromyography (EMG) data were collected from the m. biceps femoris (BF, the prime mover in this task [13,14]) to assess the latency of the first response to the obstacle [14]. Two self-adhesive Ag-AgCl electrodes (Tyco Arbo ECG) were placed longitudinally on the belly of the muscle, approximately 2cm apart, in accordance with European guidelines [15]. The EMG signals were sampled at 2400Hz (ZeroWire®, Aurion S.r.l., Italy) and recorded synchronously with the marker data.

Auditory Stroop task [12]

Participants listened to the words "high" or "low" in Dutch, presented in either a high or low pitch, with an interstimulus interval of 1.5s. They had to indicate verbally which tone was presented as quickly as possible. The stimulus was congruent when the word and pitch matched and incongruent when they did not. An integrated 16-bit sound card and headphone with microphone were used (Whitcom® PC Headphone) and both stimulus and response were recorded synchronously with the marker and EMG data at a sample rate of 2400Hz.

Protocol

Both the primary and the secondary task were practiced before the experiment started. Five obstacle avoidance practice trials were performed, and the auditory Stroop task was practiced until the subject felt comfortable with it while in a standing position and during walking on the treadmill. The actual experiment

consisted of four series of 15 obstacle avoidance trials each. All participants performed the first and fourth series as a single obstacle avoidance task. The second and third series were performed in conjunction with a the auditory Stroop task (dual-task condition). Hence, each condition (single and dual task) comprised 30 trials. The participants were instructed not to prioritize any of the tasks, but to try their hardest to perform both tasks as well as possible.

Data analysis

Failures on the obstacle avoidance task were noted during the experiment and post-hoc verified on the basis of the marker position recordings. Failure rates (the number of failed trials divided by the total number of trials) were calculated for each step cycle phase in both the single-task and the dual-task condition.

EMG activity was full-wave rectified and low-pass filtered at 25Hz (zero lag, 4th order Butterworth filter). For each participant and each task condition, onset latencies of the EMG activity were determined by means of a computer algorithm (Matlab® software, version 7.4.0, The Mathworks Inc., US) and visual inspection. The average EMG activity of the stride preceding obstacle release of 25 trials was calculated and used as the background (control) activity during unperturbed walking. The response time was defined as the time between obstacle release and the instant at which EMG activity during the obstacle avoidance stride exceeded the average control activity plus 2 SDs (Figure 1A). The response amplitude was calculated as the average amplitude over 100ms following BF onset [13,16]. The amplitudes were normalized with respect to the maximum average background activity during the whole step cycle in the single-task condition. A similar procedure was performed to calculate and normalize the average background activity in the 100ms following the BF response onset.

To assess VRTs (verbal response times) on the Stroop task, the signals of both the stimulus and the verbal response were full-wave rectified and low-pass filtered at 40Hz (zero lag, 4th order Butterworth filter). For each participant, VRTs were calculated as the time between the stimulus onset and the response onset using a custom made computer algorithm (Matlab® software). As VRT is determined by both task characteristics as well as the strategy used, speed-accuracy trade-offs have to be considered [17]. Quick responses usually result in more failures, whereas slower responses are often more successful. Use of a composite score ((100xaccuracy)/VRT) [17] makes it possible to reckon with both speed and accuracy for all congruent and incongruent stimuli. Accuracy was defined as the percentage correct responses given with no response being

treated as a failure. Composite scores were calculated for the stimuli presented prior to, during and just after obstacle crossing, representing the timing of the secondary task with respect to obstacle release (OR, Figure 1C). The last stimulus and its response before obstacle release, was defined as prior to obstacle crossing (OR-1.61±0.11s). If the response was given during perturbed walking, the stimulus was defined as during obstacle crossing (OR+0.07±0.13s). The first stimulus during the recovery from avoiding the obstacle, was defined as just after obstacle crossing (OR+1.48±0.11s).

Statistical analysis

Failure rates were assessed using binary logistic regression with task condition as categorical factor (single task as reference category, α=0.05) in Egret® for Windows (version 2.0.31). Paired t-tests were used to test for differences in EMG outcomes between task conditions. Repeated measures ANOVAs with post-hoc pairwise comparisons were used to identify differences between the composite scores. Within-subjects factors were Timing (prior to, during or just after obstacle crossing), and Congruency (congruent or incongruent stimulus).

These analyses were performed in SPSS (SPSS® 12.0.1: SPSS Inc., Chicago, Illinois, USA). Means are presented with their standard errors (SE). The level of significance was set at 0.05.

To identify a difference of 20ms in the mean BF response time between the single and dual-task condition a sample size of 14 subjects would be needed (β= 0.9, α=0.05).

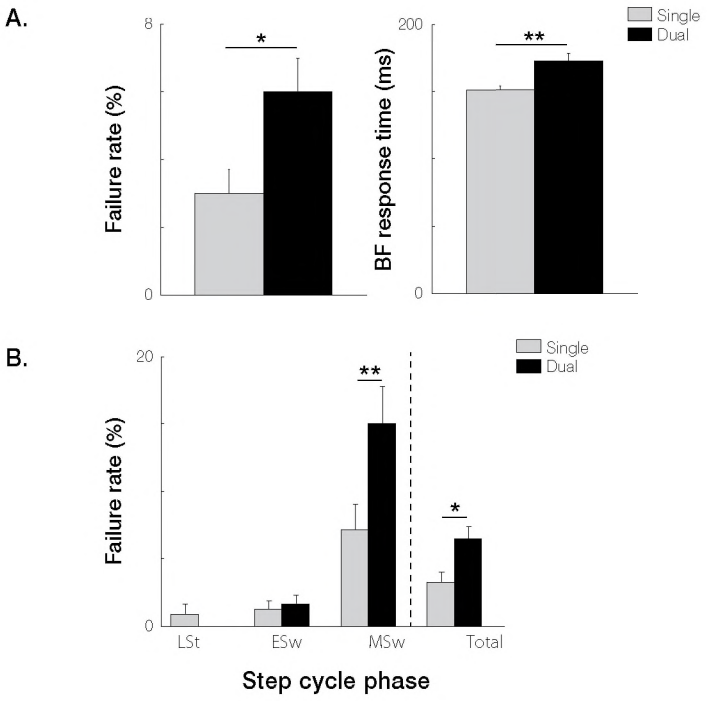
Results

Failure rate

As shown in Figure 2A, a significant increase in overall failure rate was observed when the cognitive secondary task was added to the obstacle avoidance task (3±1% vs. 6±1% in single and dual task; p=0.03). Almost all failures were made when time pressure was high, i.e. in MSw (p<0.001) compared to LSt, both in the single and dual-task condition. Within this phase the failure rate increased from 7% (single task) to 14% in the dual-task condition (p<0.01; Figure 2B).

Figure 2 Effect of a secondary cognitive task on **A**. total failure rate and BF response times, and **B**. failure rate per step cycle phase

LSt = Late Stance, ESw = Early Swing, MSw = Mid Swing. Sign. diff. between single- and dual-task condition: *$p<0.05$, **$p<0.01$



EMG outcomes

When obstacle avoidance trials were performed as a single task, BF response times were on average (±SE) 151±3.3ms. In the dual-task condition these response times significantly increased to 172±5.7ms. ($t_{1,18}$=-7.17, $p<0.001$, Figure 2A). BF response times increased in all participants and a strong correlation was observed between the individual response times in the single and dual-task condition (r=0.9, $p<0.001$). No differences between single and dual-task conditions were found in normalized response amplitude (single task: 143±32%, dual task: 139±31%; $t_{1,18}$=0.52, p=0.61) and in normalized background activity (24±2.6% vs. 25±2.5%; $t_{1,18}$=-0.38, p=0.71).

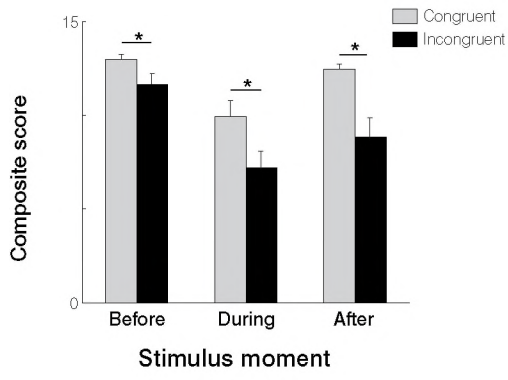
Auditory Stroop task: composite scores

The analyses revealed both main effects of Timing ($F_{2,17}$=21.7, p<0.001), and Congruency ($F_{1,18}$=27.1, p<0.001) and an interaction effect between these factors ($F_{2,17}$=4.44, p=0.03). Overall, total performance on the secondary task was worse during obstacle crossing (8.6±0.84) compared to before (12.3±0.39, p<0.001) and after obstacle crossing (10.6±0.60, p<0.001). Furthermore, the performance on the first stimulus after obstacle crossing was still worse as compared to the last stimulus prior to obstacle release (p=0.003).

Overall, incongruent stimuli resulted in lower composite scores than congruent stimuli (before: $t_{1,18}$=2.61, p=0.02; during: $t_{1,18}$=5.20, p<0.001; after: $t_{1,18}$=5.20, p=0.001; Figure 3). The congruent-incongruent difference in composite scores was significantly larger for stimuli during obstacle crossing compared to the stimuli prior to obstacle release (mean(±SE) difference: 3.7±0.58; p<0.001). The congruent-incongruent difference in composite scores for the stimuli after obstacle crossing was still larger than for stimuli prior to obstacle crossing (1.7±0.42; p=0.003), but smaller than during crossing (2.1±0.35; p<0.001).

Figure 3 Effect of stimulus timing on composite scores for the secondary cognitive task for congruent (word and voice pitch match) and incongruent stimuli (word and voice pitch do not match)

Composite score was computed as (100xaccuracy)/verbal response time. *: sign. diff. with congruent stimuli (p<0.05)



Dual-task interference

To assess whether the participants acted upon the instruction to emphasize performance on both tasks, we compared the change in each of the tasks. Therefore, we looked at the individual differences between BF response times in single-task and dual-task condition for the obstacle avoidance task, and at the individual differences between the composite scores before and during obstacle release for the secondary task. A decrement was observed in both the obstacle avoidance task and the secondary task for all subjects, indicating that they indeed followed the instruction.

Discussion

The aim of this study was to investigate dual-task interference during time-critical obstacle avoidance while participants were instructed to perform as well as possible on both the primary obstacle avoidance task and the secondary cognitive task. This study clearly showed that performing the two tasks simultaneously affects the performance on both tasks. The responses to suddenly appearing obstacles during gait were slower, but not weaker, and were less successful when there was little time to react. The performance on the cognitive task was affected too, especially during and just after obstacle crossing.

These findings are in agreement with previous studies that also demonstrated affected obstacle avoidance [3-9] or secondary task performance under dual-task conditions [10,11]. As most studies mainly reported detrimental effects on the primary task, this may be interpreted as evidence for a 'posture second' strategy, in which the secondary task is prioritized over the primary motor task. Such a strategy could be the result of (a lack of) instruction regarding task prioritization. In the present study, however, we explicitly instructed participants to try their hardest to keep up performance on both tasks. The resulting data do not support a 'posture second' strategy, as we observed dual-task interference in both the primary and the secondary task. It should be pointed out that the most pronounced differences between single- and dual-task conditions were found for the most difficult situations, i.e. when there was very little time to react to the obstacle and when incongruent stimuli were presented, whereas differences were more subtle for 'easy' obstacles and congruent stimuli. This stresses the need for challenging gait tasks and sensitive outcome measures to study dual-task interference in healthy populations.

The observation that during obstacle crossing, dual-task interference on the cognitive secondary task was more pronounced in responses to incongruent compared to congruent stimuli is reminiscent of the work on response inhibition of Redfern et al. [18]. The difference in performance between congruent and incongruent stimuli can be used as a measure for the ability to inhibit the processing of irrelevant auditory information. A larger difference is thought to indicate more difficulty in response inhibition, as a process that imposes high demands on attentional capacity. Hence, in the present experiment, participants had difficulties inhibiting inadequate verbal responses during and, to a lesser extent, after obstacle crossing. These findings demonstrate that even in our group of healthy senior participants, additional attentional resources (needed for response inhibition) are not only required for obstacle crossing, but also for recovering from an obstacle crossing step.

The senior participants in the present study (60±4.7 years) were healthy and not yet at risk of falling, thereby limiting generalization to populations who are at risk of falling such as elderly with physical or cognitive impairments. However, it seems likely that the results of this experiment would be even more pronounced if the participants were persons who are indeed at risk of falling. Future studies should expand on the present results by assessing a time-critical obstacle avoidance task under dual-task conditions in such populations.

The present study demonstrated a useful and sensitive method to assess dual-task interference in time-critical obstacle avoidance during gait. It is suggested that the changes in avoidance reactions found when dual-tasking add to an increased risk of tripping or falling when attention is divided during walking. This even seems to be the case for a group of people who are normally not considered being at risk of falling.

References

1. Faulkner KA, Redfern MS, Cauley JA, Landsittel DP, Studenski SA, Rosano C et al.: **Multitasking: association between poorer performance and a history of recurrent falls.** *J Am Geriatr Soc* 2007, 55: 570-576.
2. Weerdesteyn V, Nienhuis B, Duysens J: **Advancing age progressively affects obstacle avoidance skills in the elderly.** *Hum Mov Sci* 2005, 24: 865-880.
3. Chen HC, Schultz AB, Ashton-Miller JA, Giordani B, Alexander NB, Guire KE: **Stepping over obstacles: dividing attention impairs performance of old more than young adults.** *J Gerontol A Biol Sci Med Sci* 1996, 51: M116-M122.
4. Harley C, Wilkie RM, Wann JP: **Stepping over obstacles: attention demands and aging.** *Gait Posture* 2009, 29: 428-432.
5. Kim HD, Brunt D: **The effect of a dual-task on obstacle crossing in healthy elderly and young adults.** *Arch Phys Med Rehabil* 2007, 88: 1309-1313.
6. Siu KC, Lugade V, Chou LS, van DP, Woollacott MH: **Dual-task interference during obstacle clearance in healthy and balance-impaired older adults.** *Aging Clin Exp Res* 2008, 20: 349-354.
7. Weerdesteyn V, Schillings AM, van Galen GP, Duysens J: **Distraction affects the performance of obstacle avoidance during walking.** *J Mot Behav* 2003, 35: 53-63.
8. Brown LA, McKenzie NC, Doan JB: **Age-dependent differences in the attentional demands of obstacle negotiation.** *J Gerontol A Biol Sci Med Sci* 2005, 60: 924-927.
9. Menant JC, St George RJ, Fitzpatrick RC, Lord SR: **Impaired depth perception and restricted pitch head movement increase obstacle contacts when dual-tasking in older people.** *J Gerontol A Biol Sci Med Sci* 2010, 65: 751-757.
10. Schrodt LA, Mercer VS, Giuliani CA, Hartman M: **Characteristics of stepping over an obstacle in community dwelling older adults under dual-task conditions.** *Gait Posture* 2004, 19: 279-287.
11. Siu KC, Catena RD, Chou LS, van DP, Woollacott MH: **Effects of a secondary task on obstacle avoidance in healthy young adults.** *Exp Brain Res* 2008, 184: 115-120.
12. Shor RE: **An auditory analog of the Stroop Test.** *J Gen Psychol* 1975, 93: 281-288.
13. Hofstad CJ, Weerdesteyn V, van der Linden H, Nienhuis B, Geurts AC, Duysens J: **Evidence for bilaterally delayed and decreased obstacle avoidance responses while walking with a lower limb prosthesis.** *Clin Neurophysiol* 2009, 120: 1009-1015.
14. Weerdesteyn V, Nienhuis B, Geurts AC, Duysens J: **Age-related deficits in early response characteristics of obstacle avoidance under time pressure.** *J Gerontol A Biol Sci Med Sci* 2007, 62: 1042-1047.
15. Hermens HJ, Freriks B, Merletti R, Hägg GG, Stegeman D, Blok J, Rau G, Disselhorst-Klug C: *SENIAM 8: European Recommendations for Surface ElectroMyoGraphy.* Enschede, The Netherlands: Roessingh Research and Development b.v.; 1999.
16. Queralt A, Weerdesteyn V, van Duijnhoven HJ, Castellote JM, Valls-Sole J, Duysens J: **The effects of an auditory startle on obstacle avoidance during walking.** *J Physiol* 2008, 586; 4453-4463.
17. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM: **Dual-tasking effects on gait variability: the role of aging, falls, and executive function.** *Mov Disord* 2006, 21; 950-957.
18. Redfern MS, Jennings JR, Mendelson D, Nebes RD: **Perceptual inhibition is associated with sensory integration in standing postural control among older adults.** *J Gerontol B Psychol Sci Soc Sci* 2009, 64: 569-576.

5

NSAIDs and the risk of accidental falls in the elderly

A systematic review

Hegeman J, van den Bemt BJ, Duysens J, van Limbeek J: **NSAIDs and the risk of accidental falls in the elderly: a systematic review.** *Drug Saf* 2009, **32:** 489-498.

Abstract

Accidental falls, especially those occurring in the elderly, are a major health and research topic nowadays. Besides environmental hazards and the physiological changes associated with ageing, medication use (e.g. benzodiazepines, vasodilators and antidepressants) and polypharmancy are significant risk factors for falling as well. Exposure to NSAIDs has been associated with accidental falls too, although information on this area is less consistent. Therefore, the main goal of this review is to provide an updated overview of all the evidence published on risk of falling due to NSAID use so far. A systematic literature search for material published between 1966 and March 2008 in PubMed, EMBASE, Cochrane Database of Systematic Reviews, Exerpta Medica, Current Contents, and Science Citation Index was combined with a check of the reference lists of all the retrieved articles. Validity and data extraction of the eligible articles was assessed by adapted criteria, based on checklists that were originally developed to assess case-control or cohort studies. From the 16 selected articles, two studies were rejected due to clustering of data and one was excluded because it contained the same data as that in one of the included articles. None of the articles retrieved included a randomized controlled trial. The remaining 13 studies all showed some lack in completeness of their statistical methods, and much variation in reporting of effects. The overall mean age was high in the study populations, leaving the results to be poorly generalizable to a larger population and other age categories. Despite these imperfections, all studies showed an increased risk of falling due to NSAID use (four significant, nine non-significant), and a tendency towards an increased fall risk with NSAID exposure could be noted. The results shown in the present review suggest that an increased risk for accidental falls is probable when elderly individuals are exposed to NSAIDs. The studies with the highest quality show that the community-dwelling elderly in particular appear to be at higher risk. This review can serve as a comprehensive overview of the published evidence on fall risk of elderly individuals attributable to the use of NSAIDs, and as an inducement for future research.

Accidental falls

With the number of elderly steadily increasing, and their mean age rising, the (physical) problems that come with age will need more and more attention. Accidental falls, for example, have become a major health and research topic in terms of causes, consequences, and prevention, and 400 potential risk factors have been identified already [1-5]. A crude way to classify these risk factors is the segmentation into intrinsic and extrinsic factors [6,7]. Since this segmentation is still more or less ambiguous, the Effective Health Care Bulletin [1] managed to classify potential risk factors for falls and injury into five classes: medication related factors, changes and medical conditions associated with ageing, environmental hazards, lack of exercise, and nutrition.

Medication-related risk factors for accidental falls

Medication-related factors comprise the use of drugs such as benzodiazepines, vasodilators, antidepressants, NSAIDs (non-steroidal anti-inflammatory drugs), and polypharmacy [8-12]. A Canadian study showed that 27% of the elderly individuals (>65 years of age) hold a current or recent NSAID prescription [13]. Common adverse effects of NSAIDs include gastrointestinal and central nervous system problems. The latter consist of dizziness, headaches, mood alteration and confusion [14], consequently putting elderly individuals at a greater risk for accidental falls. The focus of this review will be on NSAID exposure as a falls risk factor in particular.

Many researchers have studied the risk factors associated with medication-related falls [5,13,15]. Russell et al. [11], for instance, studied 300 community-dwelling individuals, and identified polypharmacy as a risk factor for falls in 79% of the admissions to the emergency department. However, Ziere et al. [16] showed that polypharmacy itself is not a risk factor for falling unless a drug known to increase the risk of falls is part of the drug regimen. In fact, the odds for falling increased with 42% when drugs known to increase fall risk (e.g. benzodiazepines) were used; from 1.3-fold when one such drug was used, to 2.5-fold when two such drugs were used concomitantly, compared to the falls risk when no drugs known to increase fall risk were used.

The NSAIDs were not considered to be a drug class associated with an increased fall risk. Nevertheless, there have been a few attempts to study the relationship between other specific drug classes and falls, including some on NSAIDs. In 1999, Leipzig et al. [17] published a systematic review and meta-analysis on cardiac and

analgesics drugs. The authors found a slight non-significant increase in fall risk in elderly individuals exposed to NSAIDs. However, since then, several new studies have appeared and therefore there is a need for an updated version. Our goal is to provide an updated systematic review of all studies published thus far that present odds ratios (ORs) for the risk of falls due to NSAID use.

Study identification and selection

Medical subject headings and text words were used to perform a systematic search for material published between 1966 and 31 March 2008. Our core search terms were 'accidental falls' or 'falls', combined with 'anti-inflammatory non-steroidal agents/drugs' or 'NSAIDs' or 'drugs'. This way a total of 995 articles was retrieved from the electronic databases PubMed and EMBASE, used as the primary databases for our search. The Cochrane Database of Systematic Reviews as well as the databases Excerpta Medica, Current Contents, and Science Citation Index were secondary databases and revealed no new material.

Studies were eligible for inclusion if they were published in the English, German or Dutch language. They also had to involve NSAIDs and present an odds ratio (OR) for accidental falls, or percentages or numbers of those who had experienced falls with NSAID exposure. Two reviewers independently screened titles and abstracts on these inclusion criteria. After administration of these criteria, full-text copies of the remaining studies were obtained. In case a study was included but lacked relevant data, first authors were asked to provide the raw data on numbers of those who had and had not experience falls with and without the use of NSAIDs.

Amongst the 995 articles retrieved, there were no randomized controlled trials, controlled trials and highly controlled trials, controlled before-and-after studies nor interrupted time-series studies. Only one systematic review with meta-analysis on cardiac and analgesic drugs was found [17], and its references were used to check suitability for our review.

Methodological evaluation

Based on checklists that were originally developed to assess case-control or cohort studies, we formulated adapted criteria as described in the following two

sections [18,19]. Validity and data extraction of the articles were assessed by means of these criteria, and were scored according to four levels: sufficient [++], moderate [+], insufficient [-], or inapplicable [o].

Criteria for validity assessment

V1: This criterion tested whether there was sufficient controlling for possible confounders. Confounders had to be identified in the article, and the results had to be adjusted for them. For this review, relevant possible confounders were: age, gender and co-morbidity.

V2: The selection criteria for cases and the rationale for controls were tested. Cases were persons who experienced one or more accidental falls. Controls were defined as persons who had not experienced an accidental fall.

V3: We judged the selected study design in relation to the study aim. A cohort study (prospective / historical) was considered appropriate when all persons who were using NSAIDs were included and, thereupon, for a fixed period of time, the number of accidental falls was observed and counted. A case-control study was suitable when NSAID exposure was checked after all accidental falls were counted in a defined period of time.

V4: This criterion tested whether appropriate measures were taken to address potential sources of bias. The sources of bias can be defined as a distortion of evidence or data that arise from the way that the data are collected. Sources that were considered relevant for this review were selection bias and information bias. Selection bias was defined as the composition of the study groups showing failures. Information bias was defined as weakness in the measurement of the medication exposure in the study groups.

V5: Statistical methods related to study design were evaluated. The emphasis was on matching, group comparison, control for confounding and handling of missing data. Logistic regression, Mantel Haenszel technique or stratification of the OR were considered adequate statistical methods.

Criteria for data extraction

D1: This criterion tested whether the inclusion and exclusion criteria were described. Whether the base population from which the study groups were selected was described properly was also assessed.

D2: Appropriate reporting of effects in terms of statistical (ORs with 95% confidence interval [CIs]) as well as quantitative measures (e.g. number of cases and controls) were assessed in this criterion.

D3: It was judged if control for confounding was applied on the data by means of showing stratified adjusted odds ratios.

D4: Description of the exposure was assessed in this criterion. We defined two levels of description. First, extensive (E): mention of specific drugs with their dose. Second, simple (S): NSAIDs are only mentioned as a group, without any information on dose.

D5: This criterion tested whether the results of the study could be generalized to a larger population, including different age categories.

Two reviewers (JH and BvdB) independently evaluated the quality of the selected articles using the structured checklist and a data-collection form. To extract corresponding data, NSAIDs were defined not to be equivalent to analgesics or aspirin (acetylsalicylic acid). The definition for an accidental fall used was the one provided by the Prevention of Falls Network Europe (ProFaNE), i.e. "an unexpected event in which the participant comes to rest on the ground, floor or lower level" [6].

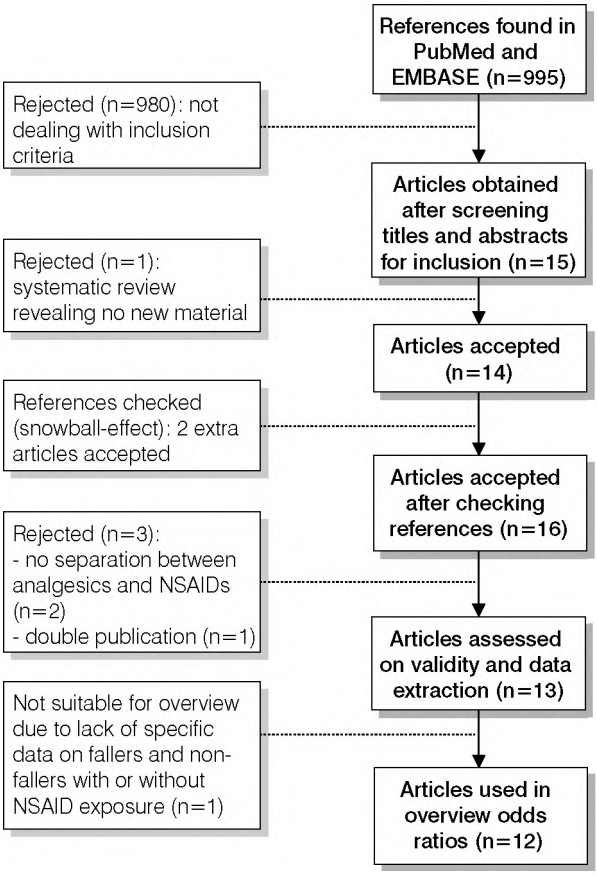
First round agreement was achieved in six articles. The rest were reassessed until both reviewers reached consensus.

Overview of research on NSAIDs and accidental falls

The initial 995 studies that were retrieved from the electronic databases were reduced to 15 articles that met our inclusion criteria for detailed data abstraction (Figure 1). We divided this selection into 2 groups; observational studies (n=14) and systematic reviews (n=1). The studies used in the systematic review revealed no new articles compared with those already retrieved, whereas checking the references of the 14 observational studies yielded another 2 articles that met the inclusion criteria for our review. From this total of 16 selected articles, 3 studies were rejected. This was because of clustering of data on analgesics together with NSAIDs in two articles [20,21] and one was excluded because it contained the same data as that in on e of the included articles [22]. All together, these rejections resulted in 13 studies [23-35] eligible for our review.

Table 1 identifies differences in settings, sample size and characteristics of the populations and study designs. What is most striking is the large variety in sample sizes and the overall high mean age. In all studies, over 50% of those who had experienced falls were female. In two studies [24,28], significantly more of

Figure 1 Flowchart of the selection and inclusion of the articles



the cases were females than in the control group; in one of these studies [24], the cases were significantly older than the control group as well. Of the 13 eligible studies, there were 9 case-control studies, 3 prospective studies, and one cross-sectional study. Six studies involved community-dwelling persons; the remaining studies investigated accidental falls in persons living in a long-term care facility.

Table 1 Differences in settings, sample size, and characteristics of the populations and study designs

[a] Odds ratio adjusted for these potential confounders
[b] Significant difference between cases and controls
Ca = cases; Co = controls; CD = community dwelling; LTC = long-term care facility.

First author	Study design	Study setting	Sample size	NSAID use	Mean age	% female	Confounders[a]
Kerman [25] (1990)	Case-control	LTC	Ca: 57 Co: 90	Ca: 30 Co: 32	Ca: 87.2 Co: 85.5	Ca: 79 Co: 87	-
Lipsitz [28] (1991)	Case-control	LTC	Ca: 70 Co: 56	Ca: 21 Co: 13	Ca: 87.0 Co: 87.0	Ca: 73[b] Co: 48	Age, gender, co-morbidity
Myers [31] (1991)	Case-control	LTC	Ca: 184 Co: 184	Ca: 22 Co: 9	Ca: 83.0 Co: 80.7	Ca: 68 Co: 76	-
Ryynaänen [33] (1993)	Case-control	CD Ca: 83% Co: 97%	Ca: 380 Co: 342	Ca: 126 Co: 51	Ca: 79.1[b] Co: 73.8	Ca: 77 Co: 72	Age, co-morbidity
Yip [35] (1994)	Case-control	LTC	Ca: 71 Co: 55	Ca: 15 Co: 7	Ca: 82.3 Co: 81.7	Ca: 66 Co: 65	Age, gender, co-morbidity
Lord [29] (1995)	Prospective	CD	362 Ca: 73 Co: 289	Ca: 24 Co: 65	74.0	100	Age, co-morbidity
Koski [26] (1996)	Prospective	CD	979		>70.0	62	Age, gender
Mustard [30] (1997)	Case-control (matched)	LTC	Ca: 1486 Co: 1486	Ca: 260 Co: 234	Ca: >75.0 Co: >75.0	Ca: 78 Co: 78	Age, gender, co-morbidity
Nikolaus [32] (1999)	Prospective	CD	279 Ca: 120 Co: 159	Ca: 29 Co: 91	81.6	73	-
Kelly [24] (2003)	Case-control	CD	Ca: 2278 Co: 9112	Ca: 159 Co: 547	Ca: 78.5[b] Co: 74.5	Ca: 69[b] Co: 57	Age, gender, co-morbidity
Kallin [23] (2004)	Case-control	LTC	Ca: 301 Co: 3303	Ca: 26 Co: 187	Ca: 83.1 Co: 83.3	Ca: 66 Co: 68	Age, gender
Walker [34] (2005)	Case-control	LTC	Ca: 62 Co: 62	Ca: 30 Co: 11	Ca: 74.9 Co: 74.5	Ca: 52 Co: 50	-
Lee [27] (2006)	Cross-sectional	CD	4000 Ca: 1024 Co: 2976	Ca: 61 Co: 112	72.5	60	Age, gender

The outcomes of the assessment of validity and data extraction are presented in table 2. None of the studies complied with all ten criteria used in this assessment. From the aspect of validity, all studies show some lack in completeness of their statistical methods; correction for possible confounders was sufficiently carried out in only four studies. The selection of cases and controls, and the selected study design were adequate in all but one study.

Table 2 Outcomes of the assessment of validity and data extraction of the eligible articles

Four scoring levels were used: sufficient [++], moderate [+], insufficient [-], or inapplicable [o].
V1 = possible confounders, V2 = selection criteria cases and controls, V3 = study design related to study aim, V4 = address of potential sources of bias, V5 = statistical methods related to study design, D1 = description in- and exclusion criteria, D2 = reporting of effects, D3 = control for confounding, D4 = description of medication exposure: extensive (E) or simple (S), D5 = generalisability. See Methods for more detailed explanation of symbols.

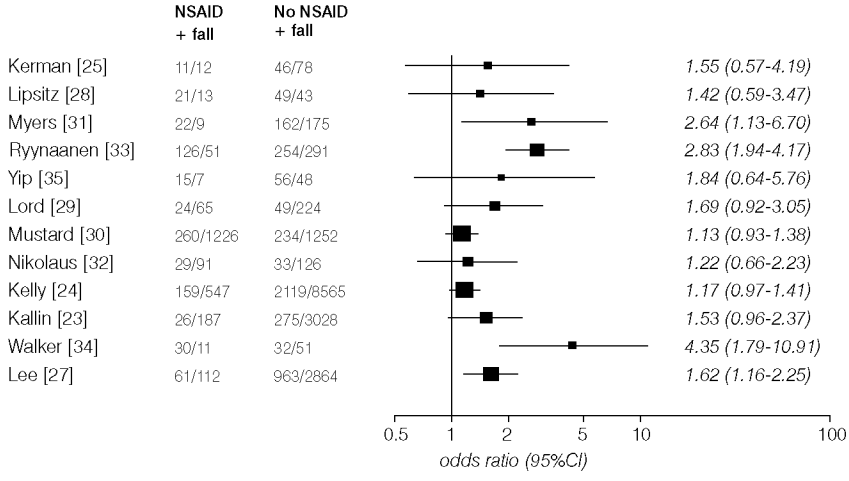
First author	V1	V2	V3	V4	V5	D1	D2	D3	D4	D5
Kerman [25]	–	++	++	+	–	+	–	–	S	–
Lipsitz [28]	+	++	++	+	+	++	++	+	S	+
Myers [31]	+	++	++	++	+	+	+	+	S	+
Ryynaänen [33]	+	++	++	++	+	+	+	–	S	+
Yip [35]	++	++	++	++	+	++	++	++	S	+
Lord [29]	+	++	++	+	+	++	+	+	S	+
Koski [26]	+	++	++	++	+	++	+	+	S	+
Mustard [30]	++	++	++	++	+	+	++	+	S	+
Nikolaus [32]	–	++	++	++	+	+	++	–	S	–
Kelly [24]	++	++	++	++	+	++	++	++	S	++
Kallin [23]	+	++	++	+	+	++	++	–	S	+
Walker [34]	–	++	++	+	+	++	++	–	E	+
Lee [27]	+	++	+	+	+	++	++	++	S	++

Data extraction showed more inconsistencies; in particular, the specification of the base population and the inclusion and exclusion criteria, and adequate reporting of effects varied greatly. Only one study presented an extensive

description of the medication exposure. The results of most studies were judged to be difficult to generalize to a larger population and different age categories. This was for the mostly as a result of the overall high mean age of the study populations.

Figure 2 shows an overview of the ORs of 12 studies with their 95% CI and was created with the benefit of StatsDirect statistical software© (version 2.6.7 [13/05/2008]); StatsDirect Ltd, Cheshire, UK). One study is not included in this final overview. It presented an OR of 1.7 (95%CI: 0.95, 3.10), but it was impossible to retrieve the raw data needed [26]. The ORs calculated in figure 2 are based on raw data on those who had experienced falls and those who had not, with and without NSAID exposure. Again, a large variety between the studies is observed; ORs, 95%CIs as well as sample sizes show vast differences. In this figure, with four studies presenting a significantly increased OR and eight studies presenting a non-significantly increased OR, a tendency towards an increased fall risk with NSAID exposure is suggested.

Figure 2 Forest plot of the odds ratios of 12 studies with their 95% confidence intervals. The black squares represent the sample sizes



Comparison with other drug classes

The main goal of this study was to provide an updated overview of all evidence published on odds ratios and falls due to NSAIDs. Thirteen studies turned out to be eligible in order to reach this goal; none of them were randomized clinical trials. Several studies presented an OR between 1 and 2. This is in the range of the ORs on accidental falls for benzodiazepines – a drug class known to increase the risk of falls – identified by Ziere et al. [16] (OR: 1.3 (95%CI, 1.0, 1.9)). In line with this finding, Leipzig et al. [36] presented an OR for accidental falls of 1.48 (1.23, 1.77) in elderly exposed to benzodiazepines. Moreover, Ensrud et al. [37] found a 51% increased risk for falling in older women using benzodiazepines. These findings imply that elderly individuals taking NSAIDs can indeed be at a higher risk for accidental falls, even at a similar level as those taking drugs well known to increase the risk of falls.

In 1999 Leipzig et al. [36] conducted a systematic review and meta-analysis on psychotropic drugs to evaluate the evidence linking these risk drugs with accidental falls in older people. They found a small association between the use of most classes of psychotropic drugs and falls, but the evidence was methodologically similar to the findings in the present review. Even though there is more knowledge about evidential value in studies nowadays, heterogeneous methodology and therefore lack of univocal results is still a common phenomenon.

Effects of variability in methodology

For the present review, it was clear that there was a large variability in the studies selected. This finding is concordant with the conclusion of Leipzig et al. [17] in their review on cardiac and analgesic drugs. The two elements all studies had in common were that they were solely based on observational data, and the high mean age of the study population (on average >75 years). Moreover, the heterogeneous methodology and diversity on many aspects of the studies was striking. Major aspects such as correction for possible confounders, sample size, and possible generalization of the outcomes to a larger population varied widely. Even the kind of populations and falls that were included showed dissimilarities. No single definition of an accidental fall was used as designated standard. One study comprised injurious falls only, thereby very likely biasing the odds ratio, since injurious falls represent just a minority of all falls in elderly populations [33].

Nevertheless, all included studies present an increased OR, and their results imply that there is a tendency towards an increased risk of accidental falls when elderly individuals are using NSAIDs.

Selection and information bias

One of our validity criteria involved the assessment of selection and information bias. After assessing all eligible articles, more possible sources of bias could be mentioned, but they did not concern all studies. First is the problem of recall bias regarding falls. There is published evidence that retrospective reporting of falls by older persons is an aspect that biases the risk of an accidental fall [38,39]. Consistent with Ganz et al. [38], Mackenzie et al. [39] concluded that retrospective self-reporting of falls is less accurate than prospective calendar-recorded fall data. They also found that an injurious fall does not, by definition, result in a better recall of falls. This is in contrast to Ganz et al. [38], whose systematic literature review showed that patients with injurious falls were more likely to recall their falls. In addition to self-reported falls, caregivers can report falls as well. The question arises whether this method of reporting is free of bias. It is likely that an accidental fall in dependent frail elderly will be remembered and reported more easily compared to a fall in more independent elderly. Bearing this in mind, the chances are that the actual number of accidental falls is higher, thereby leaving the interpretation of the results presented in the selected studies with some uncertainties.

Recall of medication use

Second, is the recall of medication use. Accurate identification of medication exposure by retrospective (self) reporting showed inconsistencies as well. Misclassification of medication exposure can either be due to medicines that are only provided or used when needed, or to a single measurement of exposure, which does not provide for the most up-to-date exposure [23,30,40]. Another aspect that interferes with accurate identification of medication exposure is the use of over-the-counter (OTC) drugs. Non-aspirin NSAIDs in particular are often used as OTC drugs. Use of these drugs is usually badly recalled [41]. Lewis et al. [41] studied use of non-aspirin NSAIDs in 1889 subjects (median age 54 years) over an 8-week period. In this period, 17.5% used prescribed non-aspirin NSAIDs, and more than twice this number (44.2%) used OTC non-aspirin NSAIDs. In line with this finding, Sawyer et al. [42] showed that taking OTC pain medication was associated with lower odds for taking prescribed pain medication (OR: 0.50,

95%CI:(0.4, 0.7)). Since in this current review none of the assessed articles showed data on OTC medication, it remains unclear in what way possible use of OTC medication might have influenced the results. In future studies, researchers should take this possible influence into account.

More complications in fall risk assessment

Another factor that complicates fall risk assessment is the use of medications in general. Up to 80% of elderly individuals suffer from chronic diseases [5,43,44], and the oldest individuals in particular usually require long-term medical treatment and several medications. Deterioration of physical and mental health status, and increasing age were found to be associated with the use of more medications [45-47]. Nevertheless, there are numerous studies that have consistently found that polypharmacy or just an increase in number of medications used by a patient can result in up to a tripling of the risk of falling [21,28,32]. Yet, Lawlor et al. [44] showed that chronic diseases and multiple pathology were more important predictors for falling than polypharmacy. They found a strong linear association between the number of drugs taken and the individual experiencing an accidental fall. However, after adjusting for chronic diseases and other potential confounding factors, this association turned out to be non-significant. Similarly, NSAIDs are mostly prescribed for (chronic) diseases of the locomotor apparatus, which themselves are a risk factor for falls [44,48,49]. Given that correction for possible confounders is generally poor in most (observational) studies on medication use and the assessment of fall risk, confounding by indication is very likely to be the backdrop of the fall risks presented.

Conclusions

The results shown in the present review suggest that an increased risk for accidental falls is probable when elderly individuals are exposed to NSAIDs. Given that correction for possible confounders is generally poor in most (observational) studies on medication use and the assessment of fall risk, confounding by indication is very likely to be the backdrop of the fall risks presented. Bearing this in mind and considering the high incidence of co-morbidity in the elderly, caution should be exerted when interpreting results of studies about

medication use and fall risk. Nevertheless, this review can serve as a comprehensive overview of the published evidence on fall risk of elderly individuals due to the use of NSAIDs thus far, and as an inducement for future research with more evidential value. Taking the incidence of falls and their consequences in the growing population of elderly individuals, exemplary future research should comprise large randomized controlled trials, along with improved prospective and extensive measuring of falls and medication use.

References

1. Oakley A, Dawson MF, Holland J, Arnold S, Cryer C, Doyle Y *et al.*: **Preventing falls and subsequent injury in older people.** *Qual Health Care* 1996, **5:** 243-249.
2. Krauss MJ, Evanoff B, Hitcho E, Ngugi KE, Dunagan WC, Fischer I *et al.*: **A case-control study of patient, medication, and care-related risk factors for inpatient falls.** *J Gen Intern Med* 2005, **20:** 116-122.
3. Lord SR, Ward JA, Williams P, Anstey KJ: **An epidemiological study of falls in older community-dwelling women: the Randwick falls and fractures study.** *Aust J Public Health* 1993, **17:** 240-245.
4. Rubenstein LZ: **Falls in older people: epidemiology, risk factors and strategies for prevention.** *Age Ageing* 2006, **35 Suppl 2:** ii37-ii41.
5. Oliver D, Daly F, Martin FC, McMurdo ME: **Risk factors and risk assessment tools for falls in hospital in-patients: a systematic review.** *Age Ageing* 2004, **33:** 122-130.
6. Skelton DA, Todd CJ: **Prevention of Falls Network Europe: a thematic network aimed at introducing good practice in effective falls prevention across Europe. Four years on.** *J Musculoskelet Neuronal Interact* 2007, **7:** 273-278.
7. Morley JE: **Falls--where do we stand?** *Mo Med* 2007, **104:** 63-67.
8. Lord SR, March LM, Cameron ID, Cumming RG, Schwarz J, Zochling J *et al.*: **Differing risk factors for falls in nursing home and intermediate-care residents who can and cannot stand unaided.** *J Am Geriatr Soc* 2003, **51:** 1645-1650.
9. Blake AJ, Morgan K, Bendall MJ, Dallosso H, Ebrahim SB, Arie TH *et al.*: **Falls by elderly people at home: prevalence and associated factors.** *Age Ageing* 1988, **17:** 365-372.
10. Daal JO, van Lieshout JJ: **Falls and medications in the elderly.** *Neth J Med* 2005, **63:** 91-96.
11. Russell MA, Hill KD, Blackberry I, Day LL, Dharmage SC: **Falls risk and functional decline in older fallers discharged directly from emergency departments.** *J Gerontol A Biol Sci Med Sci* 2006, **61:** 1090-1095.
12. Moylan KC, Binder EF: **Falls in older adults: risk assessment, management and prevention.** *Am J Med* 2007, **120:** 493-496.
13. Hogan DB, Campbell NR, Crutcher R, Jennett P, MacLeod N: **Prescription of nonsteroidal anti-inflammatory drugs for elderly people in Alberta.** *CMAJ* 1994, **151:** 315-322.
14. Weinblatt ME: **Nonsteroidal anti-inflammatory drug toxicity: increased risk in the elderly.** *Scand J Rheumatol Suppl* 1991, **91:** 9-17.
15. Hartikainen S, Lonnroos E, Louhivuori K: **Medication as a risk factor for falls: critical systematic review.** *J Gerontol A Biol Sci Med Sci* 2007, **62:** 1172-1181.
16. Ziere G, Dieleman JP, Hofman A, Pols HA, van der Cammen TJ, Stricker BH: **Polypharmacy and falls in the middle age and elderly population.** *Br J Clin Pharmacol* 2006, **61:** 218-223.
17. Leipzig RM, Cumming RG, Tinetti ME: **Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs.** *J Am Geriatr Soc* 1999, **47:** 40-50.
18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *BMJ* 2007, **335:** 806-808.
19. Geurts AC, Visschers BA, van Limbeek J., Ribbers GM: **Systematic review of aetiology and treatment of post-stroke hand oedema and shoulder-hand syndrome.** *Scand J Rehabil Med* 2000, **32:** 4-10.
20. Cumming RG, Miller JP, Kelsey JL, Davis P, Arfken CL, Birge SJ *et al.*: **Medications and multiple falls in elderly people: the St Louis OASIS study.** *Age Ageing* 1991, **20:** 455-461.
21. Neutel CI, Perry S, Maxwell C: **Medication use and risk of falls.** *Pharmacoepidemiol Drug Saf* 2002, **11:** 97-104.
22. Granek E, Baker SP, Abbey H, Robinson E, Myers AH, Samkoff JS *et al.*: **Medications and diagnoses in relation to falls in a long-term care facility.** *J Am Geriatr Soc* 1987, **35:** 503-511.
23. Kallin K, Gustafson Y, Sandman PO, Karlsson S: **Drugs and falls in older people in geriatric care settings.** *Aging Clin Exp Res* 2004, **16:** 270-276.
24. Kelly KD, Pickett W, Yiannakoulias N, Rowe BH, Schopflocher DP, Svenson L *et al.*: **Medication use and falls in community-dwelling older persons.** *Age Ageing* 2003, **32:** 503-509.

25. Kerman M, Mulvihill M: **The role of medication in falls among the elderly in a long-term care facility.** *Mt Sinai J Med* 1990, **57:** 343-347.
26. Koski K, Luukinen H, Laippala P, Kivela SL: **Physiological factors and medications as predictors of injurious falls by elderly people: a prospective population-based study.** *Age Ageing* 1996, **25:** 29-38.
27. Lee JS, Kwok T, Leung PC, Woo J: **Medical illnesses are more important than medications as risk factors of falls in older community dwellers? A cross-sectional study.** *Age Ageing* 2006, **35:** 246-251.
28. Lipsitz LA, Jonsson PV, Kelley MM, Koestner JS: **Causes and correlates of recurrent falls in ambulatory frail elderly.** *J Gerontol* 1991, **46:** M114-M122.
29. Lord SR, Anstey KJ, Williams P, Ward JA: **Psychoactive medication use, sensori-motor function and falls in older women.** *Br J Clin Pharmacol* 1995, **39:** 227-234.
30. Mustard CA, Mayer T: **Case-control study of exposure to medication and the risk of injurious falls requiring hospitalization among nursing home residents.** *Am J Epidemiol* 1997, **145:** 738-745.
31. Myers AH, Baker SP, Van Natta ML, Abbey H, Robinson EG: **Risk factors associated with falls and injuries among elderly institutionalized persons.** *Am J Epidemiol* 1991, **133:** 1179-1190.
32. Nikolaus T, Specht-Leible N, Bach M: **[Drug prescriptions and multiple falls in community-dwelling frail elderly subjects].** *Z Gerontol Geriatr* 1999, **32:** 307-311.
33. Ryynanen OP, Kivela SL, Honkanen R, Laippala P, Saano V: **Medications and chronic diseases as risk factors for falling injuries in the elderly.** *Scand J Soc Med* 1993, **21:** 264-271.
34. Walker PC, Alrawi A, Mitchell JF, Regal RE, Khanderia U: **Medication use as a risk factor for falls among hospitalized elderly patients.** *Am J Health Syst Pharm* 2005, **62:** 2495-2499.
35. Yip YB, Cumming RG: **The association between medications and falls in Australian nursing-home residents.** *Med J Aust* 1994, **160:** 14-18.
36. Leipzig RM, Cumming RG, Tinetti ME: **Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs.** *J Am Geriatr Soc* 1999, **47:** 30-39.
37. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC *et al.*: **Central nervous system-active medications and risk for falls in older women.** *J Am Geriatr Soc* 2002, **50:** 1629-1637.
38. Ganz DA, Higashi T, Rubenstein LZ: **Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval.** *J Am Geriatr Soc* 2005, **53:** 2190-2194.
39. Mackenzie L, Byles J, D'Este C: **Validation of self-reported fall events in intervention studies.** *Clin Rehabil* 2006, **20:** 331-339.
40. Ray WA, Thapa PB, Gideon P: **Misclassification of current benzodiazepine exposure by use of a single baseline measurement and its effects upon studies of injuries.** *Pharmacoepidemiol Drug Saf* 2002, **11:** 663-669.
41. Hale WA, Delaney MJ, McGaghie WC: **Characteristics and predictors of falls in elderly patients.** *J Fam Pract* 1992, **34:** 577-581.
42. Lewis JD, Strom BL, Kimmel SE, Farrar J, Metz DC, Brensinger C *et al.*: **Predictors of recall of over-the-counter and prescription non-steroidal anti-inflammatory drug exposure.** *Pharmacoepidemiol Drug Saf* 2006, **15:** 39-45.
43. Sawyer P, Bodner EV, Ritchie CS, Allman RM: **Pain and pain medication use in community-dwelling older adults.** *Am J Geriatr Pharmacother* 2006, **4:** 316-324.
44. Naughton C, Bennett K, Feely J: **Prevalence of chronic disease in the elderly based on a national pharmacy claims database.** *Age Ageing* 2006, **35:** 633-636.
45. Lawlor DA, Patel R, Ebrahim S: **Association between falls in elderly women and chronic diseases and drug use: cross sectional study.** *BMJ* 2003, **327:** 712-717.
46. Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivela SL, Isoaho R: **Use of medications and polypharmacy are increasing among the elderly.** *J Clin Epidemiol* 2002, **55:** 809-817.
47. Simons LA, Tett S, Simons J, Lauchlan R, McCallum J, Friedlander Y *et al.*: **Multiple medication use in the elderly. Use of prescription and non-prescription drugs in an Australian community setting.** *Med J Aust* 1992, **157:** 242-246.

48. Alencar MA, Arantes PM, Dias JM, Kirkwood RN, Pereira LS, Dias RC: **Muscular function and functional mobility of faller and non-faller elderly women with osteoarthritis of the knee.** *Braz J Med Biol Res* 2007, **40:** 277-283.
49. Oswald AE, Pye SR, O'Neill TW, Bunn D, Gaffney K, Marshall T *et al.*: **Prevalence and associated factors for falls in women with established inflammatory polyarthritis.** *J Rheumatol* 2006, **33:** 690-694.

6

The effect of a non-steroidal anti-inflammatory drug on two important predictors for accidental falls: postural balance and manual reaction time. A randomized, controlled pilot study

Hegeman J, Nienhuis B, van den Bemt B, Weerdesteyn V, van Limbeek J, Duysens J: **The effect of a non-steroidal anti-inflammatory drug on two important predictors for accidental falls: Postural balance and manual reaction time. A randomized, controlled pilot study.** *Hum Mov Sci* 2011, **30:** 384-395.

Abstract

Accidental falls in older individuals are a major health and research topic. Increased reaction time and impaired postural balance have been determined as reliable predictors for those at risk of falling and are important functions of the central nervous system (CNS). An essential risk factor for falls is medication exposure. Amongst the medications related to accidental falls are the non-steroidal anti-inflammatory drugs (NSAIDs). About 1-10% of all users experience CNS side effects. These side effects, such as dizziness, headaches, drowsiness, mood alteration, and confusion, seem to be more common during treatment with indomethacin. Hence, it is possible that maintenance of (static) postural balance and swift reactions to stimuli are affected by exposure to NSAIDs, indomethacin in particular, consequently putting older individuals at a greater risk for accidental falls. The present study investigated the effect of a high indomethacin dose in healthy middle-aged individuals on two important predictors of falls: postural balance and reaction time. Twenty-two healthy middle-aged individuals (59.5±4.7yrs) participated in this double-blind, placebo-controlled, randomized crossover trial. Three measurements were conducted with a week interval each. A measurement consisted of postural balance as a single task and while concurrently performing a secondary cognitive task and reaction time tasks. For the first measurement indomethacin 75mg (slow-release) or a visually identical placebo was randomly assigned. In total, 5 capsules were taken orally in the 2.5 days preceding assessment. The second measurement was without intervention, for the final one the first placebo group got indomethacin and vice versa. Repeated measures GLM revealed no significant differences between indomethacin, placebo, and baseline in any of the balance tasks. No differences in postural balance were found between the single and dual task conditions, or on the performance of the dual task itself. Similarly, no differences were found on the manual reaction time tasks. The present study has shown that a high indomethacin dose does not negatively affect postural balance and manual reaction time in this healthy middle-aged population. Although the relatively small and young sample limits the direct ability to generalize the results to a population at risk of falling, the results indicate that indomethacin alone is not likely to increase fall risk, as far as this risk is related to abovementioned important functions of the CNS, and not affected by comorbidities.

Introduction

Accidental falls have become a common occurrence in older individuals. Many risk factors and predictors for falling have been defined. One essential risk factor for falls is medication exposure. Medications linked to accidental falls in older individuals include benzodiazepines, vasodilators, antidepressants, and non-steroidal anti-inflammatory drugs (NSAIDs) [1-5]. A moderate proportion of the older individuals are exposed to NSAIDs. This population is at increased risk of adverse effects [6,7] such as gastrointestinal and central nervous system (CNS) problems. The latter have been observed during in about 5% of the patients' treatment with all NSAIDs, but their effects are more common during treatment with indomethacin [8]. Most commonly reported complaints are dizziness, headaches, drowsiness, mood alteration, and confusion [9].

After reviewing postural balance and drug response, Swift [10] concluded that postural sway appears to be a moderately sensitive indicator of the central sedative effects for a variety of drugs. As impaired balance and increased reaction time are important predictors for falls [11], use of NSAIDs may consequently put older individuals at a greater risk for accidental falls. A recent systematic review demonstrated that there is indeed a tendency towards an increased risk for falling in older individuals using NSAIDs [12]. However, the evidence from previous epidemiological research is not conclusive and only provides information on associations rather than causal relationships. Although three experimental studies investigated the effect of indomethacin on reaction time and postural balance [13-16], the results are inconsistent. Some of the discrepancies may be related to the selection of outcome measures, and to the populations and indomethacin doses that were studied. Therefore, there is a need to reinvestigate this question studying reaction time and postural balance, using more reliable outcome measures, and the highest dose of indomethacin ever studied in similar research. This randomized controlled trial studied the effect of a high indomethacin dose in healthy middle-aged individuals on two important predictors of falls: postural balance and reaction time. Based on the results of previous research we hypothesized that indomethacin will impair both postural balance and manual reaction time.

Methods

Participants

Twenty-two persons (mean age 59.5±4.7 years) volunteered to participate in this study. Volunteers were recruited from several hobby clubs in the Nijmegen region (NL). Inclusion criteria were the absence of any known serious neurological, orthopaedic, or cognitive dysfunction; age between 50–70 years, and no use of any NSAID in the 3 days prior to the measurement day. Participants were excluded if they suffered from conditions considered a contra-indication for exposure to indomethacin, had hearing problems, had poor knowledge of Dutch, had a bodyweight in excess of 100 kg, or used any (prescribed) medication that interfered with indomethacin, postural balance or reaction time. All participants provided written informed consent in accordance with the Declaration of Helsinki. This study was approved by the regional ethics committee of Arnhem and Nijmegen, and the Dutch Competent Authority.

Figure 1 shows a flow diagram displaying the progress of all participants through the trial. Indomethacin was randomly allocated to 12 participants for the first measurement. One participant dropped out before the first measurement due to adverse effects of indomethacin. Another participant, assigned to placebo, declined without reason to further participation prior to the first measurement. Of the remaining 20 participants (nine females; mean age 60±4.6 years), eight reported side effects when exposed to indomethacin, one of them also reported a headache when exposed to the placebo. Drowsiness, headache, and nausea were mostly reported. The performance of the participants with side effects did not differ from those without reported side effects.

Seven participants used prescribed medication besides the study medication and were all accustomed to it. A list of medication used by these participants is presented in Table 1. A pharmacist determined that none of these medications were considered to lead to problems of any kind when taken simultaneously with indomethacin.

Study protocol

A crossover design (Figure 2) was selected for this double-blind, randomized, placebo-controlled pilot study. Three measurements were planned with a week interval each to completely wash out the medication before the next measurement. Each measurement consisted of a set of balance tasks, as well as a simple and choice manual reaction time task. Between and within participants, the sequence

Figure 1 Flow chart showing the progress of all participants through the trial

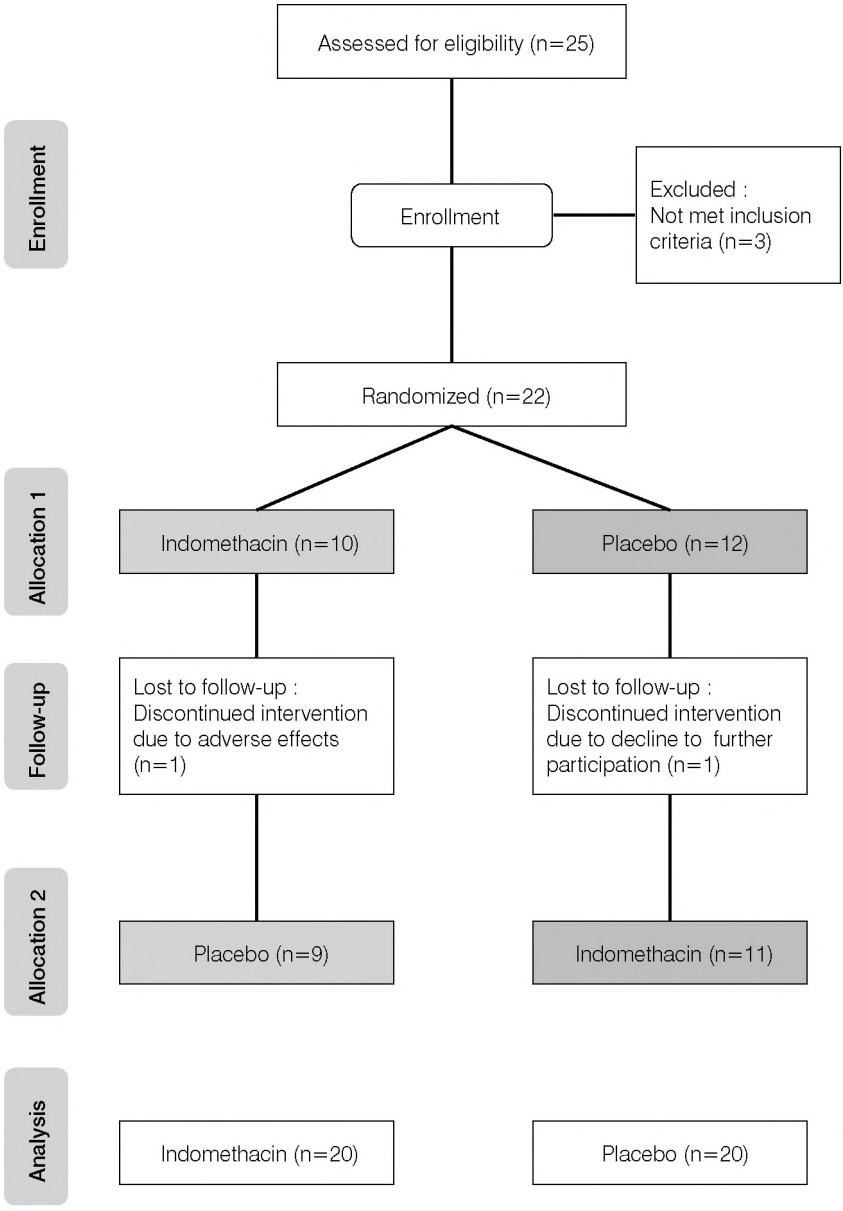


Table 1 Medication used by participants in the study

N = number of participants using medication from this medication class

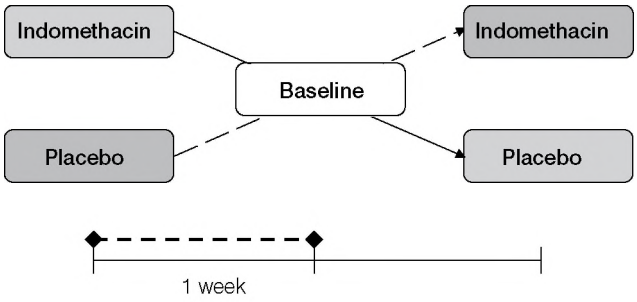
Medication class	N	Name (ATC-code)
Proton pump inhibitors	1	Lansoprazol (A02BC03)
Blood glucose lowering drugs, excl. insulin	1	Metformin (A10BA02), tolbutamide (A10BB03)
Platelet aggregation inhibitors, excl. heparin	1	Acetylsalicylic acid (B01AC06)
Diuretics	1	Hydrochlortiazide (C03AA03)
Beta blocking agents, non-selective	2	Propanolol (C07AA05)
Beta blocking agents, selective	3	Metoprolol (C07AB02)
Selective calcium channel blockers with mainly vascular effects	2	Amlodipine (C08CA01)
ACE inhibitors, plain	2	Lisinopril (C09AA03)
Angiotensin II antagonists, plain	1	Losartan (C09CA01)
Lipid Modifying Agents, plain	3	Simvastatine (C10AA01), Atorvastatine (C10AA05)
Anti-thyroid preparations	1	Carbimazole (H03BB01)
Adrenergics and other drugs for obstructive airway diseases	1	Salmeterol/fluticason (R03AK06)

of tasks (balance or reaction time) was randomized. In order to eliminate learning effects, training for all tasks was performed prior to the first measurement. Thereafter, intake of indomethacin or placebo for the first measurement was randomly assigned (http://www.randomization.com, second generator with random permutations) by a pharmacist and was kept concealed until all measurements and analyses were finished. Hence, both participants and researcher were blinded for the assigned intervention sequence throughout the whole study.

Indomethacin 75 mg slow-release or a visually identical placebo with similar flavor (capsule consisted of lactose) was taken orally twice daily (in the morning and evening). Considering the half-life of normal release and slow-release indomethacin, we chose the slow-release form in order to limit the number of capsules the participants had to take, but still reach the desired level in the blood. The participants started their intake in the morning 2 days prior to the measurement day, taking the final capsule on the morning of the measurement, in total five capsules in 2.5 days. To prevent gastro-intestinal problems, all participants were provided with three tablets of esomeprazol 20 mg to be taken simultaneously with the capsule in the morning.

As shown in Figure 2 a baseline measurement, without any intervention, was done one week later. In this paper, the term baseline is used to describe the measurement that was done without intervention. For the final measurement, the participants that were allocated to indomethacin for the first measurement received the placebo capsules and vice versa. The participants returned their empty capsule containers on the measurement day.

Figure 2 Cross-over design



Balance tasks: Equipment and procedure

Balance assessment was conducted using a firmly secured force platform (custom made), consisting of two separate aluminum plates, each placed on three force transducers that recorded the vertical ground reaction forces. Six DC-amplifiers processed the force signals which were passed through first-order low-pass filters (cut-off frequency 30 Hz). Then the signals were amplified and

stored on a personal computer after a 16-bit AD-conversion with a sampling rate of 500 Hz. Digital moment-of-force calculations were used to determine the virtual center of ground reaction forces (Center of Pressure [COP]) in the two-dimensional transverse plane for each sample. The maximum error was ±1 mm in both anterior–posterior (AP) and lateral (LAT) direction.

The participants stood barefoot on the force platform with their arms hanging alongside the trunk and their feet against a fixed foot frame. In this frame the medial sides of the heels were 8.4 cm apart and each foot was toeing-out at a 9o angle from the sagittal midline (Figure 3A). The instruction was to stand as still as possible while performing five basic tests, four of which were repeated with a dual task. In test 1 and 2 the participants stood on both legs either with eyes open (EO) or eyes closed (EC). In test 3 they stood only on one leg (the preferred one). In tests 4 and 5 the participants stood on a compliant surface (4.5 cm foam), with either eyes open or eyes closed. Except for the last test, the tests were also performed in conjunction with a cognitive task (an auditory Stroop task [17] with an interstimulus interval of 1.5 s; the dual task condition).

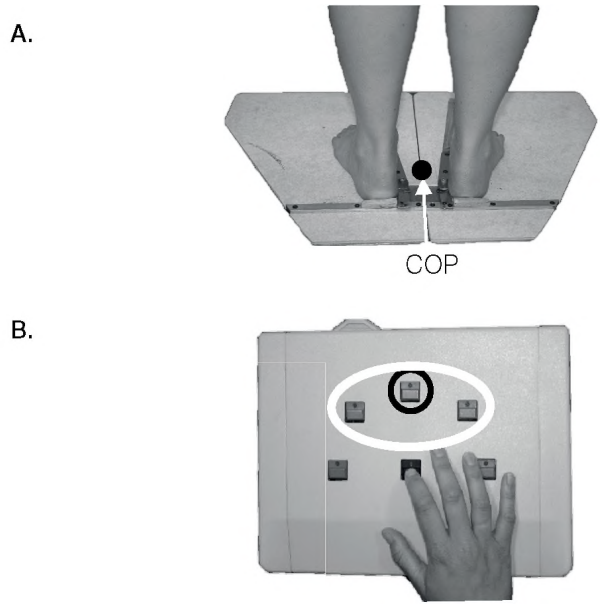
A computer screen was placed at eye level, 1 m in front of the participant, visualizing the COP in between the balance tasks. Participants were deprived of visual feedback throughout the recording of every balance task. For the dual task condition an integrated 16-bit sound card and two external speakers were used. This task required participants to listen to the words "high" or "low" in Dutch, presented in either a high or low pitch and to verbally indicate which tone was presented as soon as possible (at most 18 times per balance condition). The answers were registered by the researcher. Before the balance measurements, the cognitive task was practiced until the participant felt comfortable with it while in a standing position without paying attention to balance.

The COP signals were passed through a digital, low-pass filter (zero phase Butterworth, cut-off frequency 6 Hz). Consecutively, the root mean square (RMS) values of COP amplitude and velocity were computed in both AP and LAT direction. The RMS COP velocity was selected as the primary measure of postural balance in each direction of body sway, since it has been shown that this measure is more reliable than the RMS COP amplitude [18,19]. COP fluctuations during each condition were recorded for 30 s, except for the one-legged stance; in that condition fluctuations were recorded for 15 s. The first 5 s were always excluded from the analysis to remove any undesired starting effects. Each of the balance tasks was performed twice; the second recording with the sequence in reversed order to exclude the influence of fatigue. For each task, the mean RMS value was included in the statistical analysis.

Manual reaction time task: Equipment and procedure

The equipment consisted of a button box with one black home button and five orange target buttons (Figure 3B). Passed through a CIO-DIO24/CTR3 interface, made by Computer Boards Inc., the button box was connected to a personal computer. Signals were processed using the internal 10Mc crystal generator, which resulted in a maximum error on the reaction time of 0.1 ms.

Figure 3 Experimental setup. **A**. Force platform. COP = Center of Pressure. **B**. Manual reaction time tasks (simple: 1 target button (black circle), choice: 3 target buttons (white circle))



Simple and choice manual reaction time tasks were performed. Participants held their preferred index or middle finger on the home button and as soon as the light in the target button switched on, they had to press the target button as quickly as possible. When they were too fast (<150 ms), too slow (>1000 ms) or made a failure, a short beep reminded them to return to the home button. The failed trial was repeated at the end of the sequence. The simple task consisted of

15 trials with a single target button; the choice task comprised a total of 45 trials with three target buttons (Figure 3B). Each task was performed twice; the second series in reversed order, again to exclude the influence of fatigue. Reaction time (time between switching on of the target light and releasing the home button) as well as movement time (time between releasing the home button and pressing the target button) were recorded in milliseconds. For both tasks, the median reaction time (RT) and movement time (MT) were included in the statistical analysis.

Statistical analysis

Repeated measures GLM with post hoc paired t-test were carried out in SPSS® (version 12.0.1) to assess the effect of experimental condition on postural balance, dual task performance, as well as manual reaction time. Experimental condition (indomethacin, placebo, or baseline) was a within-subjects factor and sequence (start crossover with indomethacin or placebo) as between-subjects factor. The level of significance was set at .05.

Previous research on the effect of indomethacin on postural sway in a task with eyes open indicated increments of 21% [15] and 34% [16]. Hence it was decided that an increase of 25% in sway would be relevant. Prior data indicated that the difference in RMS velocity of postural sway in a task with eyes open between matched pairs is normally distributed with standard deviation of 2.5 mm/s. If the true difference in the mean sway between indomethacin and placebo was 2 mm/s, we needed to study 18 participants in this cross-over design to be able to reject the null hypothesis that there was no difference in postural sway between these two experimental conditions (β=0.9, α=0.05).

Results

Balance tasks

Table 2 summarizes the results of all balance tasks, both in the single and dual task condition, and presents the mean values of the RMS COP velocity (mm/s) in AP and LAT direction. Note that in the tasks where nearly significant differences were found, postural sway in the indomethacin condition was always less than in the placebo and baseline condition. Moreover, most of the differences found are within the maximum measurement error of 1 mm and are therefore of little clinical relevance. Repeated measures GLM revealed only a main effect of experimental

Table 2 Balance tasks: Root Mean Square of Center of Pressure velocity in mm/s (mean ± SD)

EO = eyes open, EC = eyes closed, AP = Anterior-Posterior direction, LAT = Lateral direction. Bold values are significantly different from baseline, underlined values are significantly different from indomethacin ($p<0.05$). *: significant difference EO-EC ($p<0.001$), †: significant difference firm-compliant surface ($p<0.001$), ¶: significant difference single-dual task ($p<0.05$). ***p*-value** = p-value of repeated measures GLM with experimental condition (Indomethacin, Placebo, Baseline) as main effect.

	Indomethacin		**Placebo**		**Baseline**		**p-value**	
	Single task	*Dual task*	*Single task*	*Dual task*	*Single task*	*Dual task*	*Single task*	*Dual task*
One leg, firm surface								
EO AP	25.00 (6.61) ¶	31.61 (21.31)	23.94 (7.05) ¶	33.46 (17.61)	23.07 (5.20) ¶	31.77 (17.12)	0.153	0.427
EO LAT	35.37 (6.12)	**40.94 (9.98)**	39.82 (12.24)	43.80 (8.50)	35.89 (7.46) ¶	44.45 (10.62)	0.162	0.002
Two legs, firm surface								
EO AP	6.71 (1.59) *	7.99 (3.47) *	7.09 (2.04) *	7.61 (2.31) *	7.16 (1.90) *	7.97 (3.07) *	0.173	0.744
EC AP	**11.40 (4.38)** ¶	12.74 (4.43)	12.34 (5.32) ¶	13.51 (5.33)	12.20 (5.29) ¶	13.44 (5.97)	0.064	0.592
EO LAT	3.43 (1.21) *	4.04 (1.87) *	3.31 (1.13) *¶	4.01 (1.53) *	3.63 (1.36) *	3.74 (1.27) *	0.290	0.275
EC LAT	**4.98 (2.09)**	5.57 (2.74)	5.17 (2.45)	5.95 (2.43)	5.51 (2.45)	5.69 (2.39)	0.082	0.216
Two legs, compliant surface								
EO AP	13.24 (2.30)*†¶	14.58 (2.16)†	13.28 (2.44) *†¶	**15.64 (3.47)†**	13.05 (2.65)*†¶	14.40 (3.09)†	0.861	0.115
EC AP	35.89 (10.19) †	-	39.08 (12.38) †	-	36.58 (11.40) †	-	0.340	-
EO LAT	6.82 (1.74) *†	7.37 (1.78)†	7.05 (1.87) *†	**7.88 (2.15)** †	6.95 (1.80) *†	7.22 (1.92) †	0.445	0.063
EC LAT	16.78 (5.36) †	-	**19.17 (7.81)** †	-	16.81 (6.44) †	-	0.057	-

condition on the COP velocity of the LAT direction of the one-legged stance balance task in the dual task condition, $F_{2,17}$ =10.87, p=0.002. As shown in Table 2, significant differences in postural sway, mostly in the AP direction, were found between the single and dual task condition. These differences were uniform across the experimental conditions. No interaction effects (sequence*experimental condition; highest $F_{2,17}$=3.31, p>0.05) or between-subjects effects (sequence) were found (highest $F_{1,18}$ =3.46, p>0.05) on all balance tasks.

Figure 4 illustrates the similarity between the experimental conditions for the two most difficult tasks, namely stance on one leg (4A) and stance on both legs on a compliant surface (4B). The other tasks yielded similar results. Note in Figure 4B that the EC task always resulted, as expected, in higher COP velocities. In all conditions the COP velocity was significantly larger with eyes closed and when standing on compliant surface (p<0.001). This difference was present both for the AP and the LAT directions. However, the differences between EO and EC tasks and on the normal and compliant surface were uniform across the experimental conditions (Table 2).

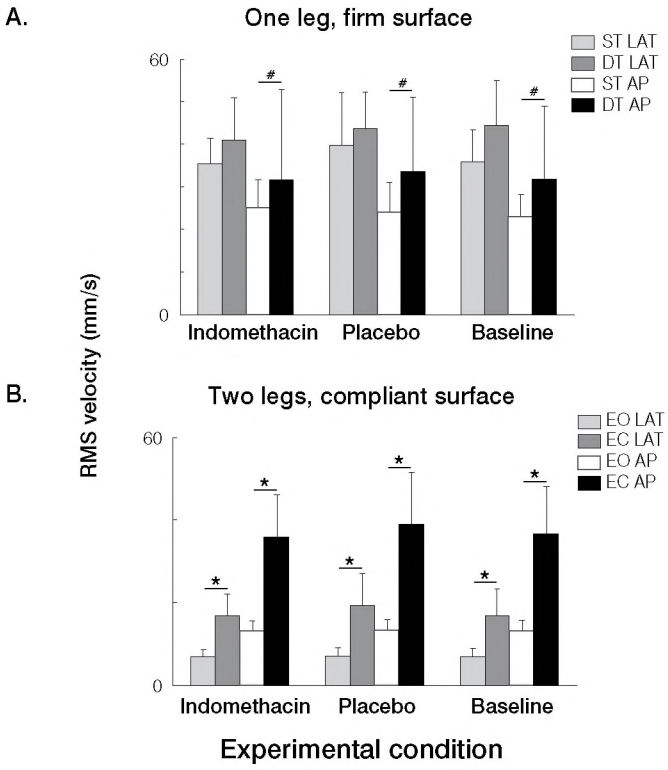
The data of one participant were excluded from the secondary cognitive task itself. Analysis of this participant's performance showed that all incongruent (voice pitch and word do not match) stimuli were answered incorrectly in each experimental condition, even though this participant had confirmed that the intention of the task was clear. Repeated measures GLM revealed no main effect of experimental condition in the percentages of correct answers given (highest $F_{2,16}$=1.57, p>0.2) of the remaining 19 participants. On average, they correctly answered on 95% of the stimuli. This was similar for all balance tasks (p>0.3).

Manual reaction time task

Repeated measures GLM yielded no main effect of experimental condition on both simple ($F_{2,17}$= 0.58, p=0.57) and choice ($F_{2,17}$=0.06, p=0.94) reaction time tasks. No interaction ($F_{2,17}$=0.05, p=0.96) or between-subjects ($F_{1,18}$=0.76, p=0.39) effects were found. In other words, indomethacin did not affect reaction time. Regardless of the experimental condition a within-subjects effect was found between the simple and choice reaction time task (p<0.02). Both RT and MT were significantly longer in the choice than in the simple reaction time task (p<0.05).

Figure 4 Population characteristics

A. Stance on 1 leg with eyes open; comparison between single and dual task. **B**. Stance on 2 legs on a compliant surface; comparison between eyes open and eyes closed. Bars represent mean (± SD) COP Velocity. ST = Single Task, DT = Dual Task, EO = Eyes Open, EC = Eyes Closed, LAT = Lateral direction, AP = Anterior-Posterior direction. *: significant difference EO-EC ($p<0.001$) #: significant difference single-dual task ($p<0.05$)



Discussion

This study investigated the effect of a high indomethacin dose on postural balance and reaction time in healthy middle-aged individuals, in the context of a possible link between NSAID exposure and an increased risk for accidental falls. We discovered no negative effect of indomethacin on either one of these CNS functions.

The present study was a double-blind, placebo-controlled randomized controlled trial (RCT), the results of which provide a high level of evidence for therapeutic interventions [20]. Given that there were no significant relevant interactions or between-subjects (sequence) effects, the randomization appeared to have been successful. Due to the crossover design every individual participated in all experimental conditions. Hence, correction was made for possible confounders such as age, gender, physical condition, and medication exposure. Another aspect of the strong methodology of our study was the fact that the participants were healthy middle-aged individuals. Even though most literature on falls describes populations of older individuals (>75 years), we deliberately chose to use middle-aged persons for our study. This group is known to use the type of medication under investigation. Furthermore, due to their age, this group of individuals was already more sensitive to medications [21], yet they did not suffer from possible (serious) comorbidities that come with increasing age. Older individuals are more sensitive to medication as well. Hence, the current results might be applicable to an older population as long as fall risk increasing comorbidities are absent.

Postural balance

The present study revealed only a small effect of indomethacin on postural balance, mainly during quiet stance with eyes closed on the firm surface. However, on all tasks there was a trend of decreased postural sway for the indomethacin condition, both in the LAT and the AP direction. This is in contrast to our expectations and to previous studies on indomethacin and postural balance. [15] studied 15 patients with rheumatoid arthritis. They measured body sway in the AP and LAT direction with eyes open and closed, after administration of indomethacin (2 days 3x25 mg followed by 1 day 3x50 mg). In comparison to placebo, a clear increase in body sway during quiet stance with eyes closed was found. However, these authors mentioned that this could be a chance finding since indomethacin could not be detected in plasma at baseline. In contrast, effects of indomethacin on postural balance in the present study are largely in line with the findings reported by Telekes et al. [16]. They performed a double-blind, randomized crossover study in 12 volunteers (aged 21–36) and concluded that a single dose of 50 or 100 mg indomethacin does not significantly affect anteroposterior body sway during 60 s quiet stance with eyes closed. These negative results are fairly robust, especially since acute studies of analgesics on healthy volunteers appear to overestimate rather than to underestimate the detrimental effects of analgesics on performance [15]. Furthermore, the present study administered, in healthy

middle-aged individuals naïve to this drug, the highest dose of indomethacin ever studied in postural balance. In contrast to previous research, the present study assessed postural balance both as a single task and while a concurrent secondary cognitive task was performed. A concurrent secondary task can interfere with the visual, vestibular, and proprioceptive regulation of postural balance. Both increased [22] and reduced [23] sway amplitudes have been reported when attention was redirected from balance control towards a secondary cognitive task, indicating that the ability to maintain balance or a postural task involves additional attentional demands [24-27]. Moreover, it has been shown that age differences in balance abilities are magnified by a concurrent cognitive task [27-29]. Hence, this implies that the dual task paradigm is useful to detect changes in postural sway. The present study showed neither significant balance changes between the experimental conditions while performing the Stroop task nor changes on the performance of this secondary cognitive task itself. Therefore, we conclude that indomethacin does not affect this aspect of cognitive functioning.

It may be argued that the lack in difference between tasks was due to the lack of sensitivity in the measurement method. However, the methods used have been sensitive enough to reveal all the expected differences between the balance tasks. The increase in COP velocity found was in the same range as that reported in previous studies [18,19,30]. Similarly, the observed increase in EC as compared to the EO condition is completely consistent with former experiments [18,30].

Considering the above mentioned evidence on the sensitivity of postural testing, our conclusion is that indomethacin itself does not negatively affect postural balance, even in more challenging situations such as performing a secondary cognitive task or standing on a compliant surface. This implies that at least the physiological systems involved in these tasks have not been affected. These also include cognitive functioning.

The fact that some participants reported feeling dizzy and lethargic when exposed to indomethacin remains unexplained. Perhaps indomethacin affects systems which would not be used to perform the present tasks, sensitive as they may be. For example, the current tests all involve only maintaining static balance whereas in daily life one encounters many situations requiring maintenance of dynamic balance. The latter involves matching visual and vestibular information; it is conceivable that indomethacin selectively affects the integration of information from these sensory sources. Another possibility is that there is interference with systems detecting self-motion 15,31,32]. Hence, it would be interesting to include dynamic balance tests in future studies on indomethacin.

Manual reaction time

The present study revealed no effect of indomethacin on manual reaction time. Previous research studying the effect of indomethacin on reaction times reported contrasting results. Linnoila et al. [14] studied choice reaction time (CRT) in 20 students exposed to a single dose of 50 mg indomethacin and compared them with 30 matched individuals who took a placebo drug. The indomethacin group showed a significant prolongation of the cumulative CRT ($p<0.05$). In contrast, Bruce-Jones [13] revealed a decrease in CRT on indomethacin to a maximum of 6.62% below baseline before dosing, as well as a significant difference in RT between indomethacin and placebo. They tested 20 individuals (>55 years) in a double-blind, placebo-controlled crossover study on CRT after administration of 25 mg indomethacin or matched placebo three times daily for 7 days. The present results, based on the intake of 75 mg indomethacin twice daily for 2.5 days, are again closest to the findings of Telekes et al. [16]. They assessed reaction time in individuals exposed to a single dose of 50 or 100 mg indomethacin in a comparable manner as the present study, and again no significant effect of this drug compared to placebo was found.

For this parameter, the possibility of lack of sensitivity in the measurement method can be excluded by the fact that our methods were sensitive enough to reveal the expected differences between the tasks assessed. Both reaction time and movement time were higher in the choice than in the simple task. Therefore, we feel justified in concluding that high doses of indomethacin do not affect manual reaction time in healthy middle-aged individuals.

Limitations

Earlier research on the effect of medications on the risk of falling mostly have studied older individuals (>75 years of age). Therefore, the participation of healthy middle-aged individuals in this study could be considered to limit the value of this study. However, a major limitation of many of the previous studies on falls in the elderly is the lack of proper correction for confounding. Therefore it is difficult to focus on single factors associated with falling. By means of using a cross-over design and a healthy middle-aged sample we corrected for possible confounders and focused on the effects of a single drug, indomethacin, which represented the group of NSAIDs.

Another limitation could be the relatively small sample size. Yet it is unlikely that a larger sample size would have yielded other results. Moreover, if a significant difference were to be found in a larger sample size with the direction of intervention

effect identified in this study, use of indomethacin would result in less postural sway, implying better postural balance.

A factor that might have influenced the performance of some participants is the occurrence of side effects from indomethacin exposure. Since we used a high daily dose for 2.5 days, the possibility that these side effects might have unblinded participants cannot be ruled out. On the other hand, this element is not unequivocal since there were also complaints by one participant when taking a placebo.

There might be limitations in the tests currently being used. Therefore, for future studies, it would be an advantage to use tests, proven sensitive enough to assess other functions of the CNS, involving behavior that is relevant to stumbles and falls. One such condition, currently under investigation, is the ability to avoid obstacles during walking. Such conditions have been used to test for analgesic effects in patients with osteoarthritis [33] but not to test reaction time to a sudden obstacle, required to avoid falls.

Conclusion

The present study has shown that a high indomethacin dose does not negatively affect postural balance and manual reaction time in a population of healthy middle-aged individuals. The relatively young sample limits the generalizability of these results to a larger population, especially those at risk of falling. However, our middle-aged population is known already to be more sensitive to medications, which is also the case in an older population. Therefore we suggest that indomethacin alone is not likely to increase fall risk in an older population, as far as this risk is related to above mentioned important CNS functions, and not affected by comorbidities.

References

1. Blake AJ, Morgan K, Bendall MJ, Dallosso H, Ebrahim SB, Arie TH *et al.*: **Falls by elderly people at home: prevalence and associated factors.** *Age Ageing* 1988, **17:** 365-372.
2. Daal JO, van Lieshout JJ: **Falls and medications in the elderly.** *Neth J Med* 2005, **63:** 91-96.
3. Lord SR, Anstey KJ, Williams P, Ward JA: **Psychoactive medication use, sensori-motor function and falls in older women.** *Br J Clin Pharmacol* 1995, **39:** 227-234.
4. Moylan KC, Binder EF: **Falls in older adults: risk assessment, management and prevention.** *Am J Med* 2007, **120:** 493-496.
5. Russell MA, Hill KD, Blackberry I, Day LL, Dharmage SC: **Falls risk and functional decline in older fallers discharged directly from emergency departments.** *J Gerontol A Biol Sci Med Sci* 2006, **61:** 1090-1095.
6. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA: **The epidemiology of chronic pain in the community.** *Lancet* 1999, **354:** 1248-1252.
7. Laine L: **The gastrointestinal effects of nonselective NSAIDs and COX-2-selective inhibitors.** *Semin Arthritis Rheum* 2002, **32:** 25-32.
8. Seideman P, von Arbin M: **Cerebral blood flow and indomethacin drug levels in subjects with and without central nervous side effects.** *Br J Clin Pharmacol* 1991, **31:** 429-432.
9. Weinblatt ME: **Nonsteroidal anti-inflammatory drug toxicity: increased risk in the elderly.** *Scand J Rheumatol Suppl* 1991, **91:** 9-17.
10. Swift CG: **Postural instability as a measure of sedative drug response.** *Br J Clin Pharmacol* 1984, **18 Suppl 1:** 87S-90S.
11. Lajoie Y, Gallagher SP: **Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers.** *Arch Gerontol Geriatr* 2004, **38:** 11-26.
12. Hegeman J, van den Bemt BJ, Duysens J, van Limbeek J: **NSAIDs and the risk of accidental falls in the elderly: a systematic review.** *Drug Saf* 2009, **32:** 489-498.
13. Bruce-Jones PN, Crome P, Kalra L: **Indomethacin and cognitive function in healthy elderly volunteers.** *Br J Clin Pharmacol* 1994, **38:** 45-51.
14. Linnoila M, Seppala T, Mattila MJ: **Acute effect of antipyretic analgesics, alone or in combination with alcohol, on human psychomotor skills related to driving.** *Br J Clin Pharmac* 1974, 477-484.
15. Saarialho-Kere U, Julkunen H, Mattila MJ, Seppala T: **Psychomotor performance of patients with rheumatoid arthritis: cross-over comparison of dextropropoxyphene, dextropropoxyphene plus amitriptyline, indomethacin, and placebo.** *Pharmacol Toxicol* 1988, **63:** 286-292.
16. Telekes A, Holland RL, Peck AW: **Indomethacin: effects on cold-induced pain and the nervous system in healthy volunteers.** *Pain* 1987, **30:** 321-328.
17. Shor RE: **An auditory analog of the Stroop Test.** *J Gen Psychol* 1975, **93:** 281-288.
18. Geurts AC, Nienhuis B, Mulder TW: **Intrasubject variability of selected force-platform parameters in the quantification of postural control.** *Arch Phys Med Rehabil* 1993, **74:** 1144-1150.
19. Lafond D, Duarte M, Prince F: **Comparison of three methods to estimate the center of mass during balance assessment.** *J Biomech* 2004, **37:** 1421-1426.
20. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S *et al.*: **Grading quality of evidence and strength of recommendations.** *BMJ* 2004, **328:** 1490.
21. Lowenthal DT: **Clinical Pharmacology.** In *The Merck Manual of Geriatrics*. Edited by Abrams WB, Berkow R. Rahway, N.J.: Merck Sharp and Dohme Research Laboratories; 1990:181-199.
22. Andersson G, Hagman J, Talianzadeh R, Svedberg A, Larsen HC: **Effect of cognitive load on postural control.** *Brain Res Bull* 2002, **58:** 135-139.
23. Swan L, Otani H, Loubert PV, Sheffert SM, Dunbar GL: **Improving balance by performing a secondary cognitive task.** *Br J Psychol* 2004, **95:** 31-40.
24. Lajoie Y, Teasdale N, Bard C, Fleury M: **Attentional demands for static and dynamic equilibrium.** *Exp Brain Res* 1993, **97:** 139-144.
25. Lajoie Y, Teasdale N, Bard C, Fleury M: **Upright standing and gait: are there changes in attentional requirements related to normal aging?** *Exp Aging Res* 1996, **22:** 185-198.
26. Marsh AP, Geel SE: **The effect of age on the attentional demands of postural control.** *Gait Posture* 2000, **12:** 105-113.

27. Shumway-Cook A, Woollacott M, Kerns KA, Baldwin M: **The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls.** *J Gerontol A Biol Sci Med Sci* 1997, **52:** M232-M240.
28. Chen HC, Schultz AB, Ashton-Miller JA, Giordani B, Alexander NB, Guire KE: **Stepping over obstacles: dividing attention impairs performance of old more than young adults.** *J Gerontol A Biol Sci Med Sci* 1996, **51:** M116-M122.
29. Maylor EA, Wing AM: **Age differences in postural stability are increased by additional cognitive demands.** *J Gerontol B Psychol Sci Soc Sci* 1996, **51:** 143-154.
30. Weerdesteyn V, Rijken H, Geurts AC, Smits-Engelsman BC, Mulder T, Duysens J: **A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly.** *Gerontology* 2006, **52:** 131-141.
31. Marigold DS, Weerdesteyn V, Patla AE, Duysens J: **Keep looking ahead? Re-direction of visual fixation does not always occur during an unpredictable obstacle avoidance task.** *Exp Brain Res* 2007, **176:** 32-42.
32. Patla AE, Vickers JN: **How far ahead do we look when required to step on specific locations in the travel path during locomotion?** *Exp Brain Res* 2003, **148:** 133-138.
33. Pandya NK, Piotrowski GA, Pottenger L, Draganich LF: **Pain relief in knee osteoarthritis reduces the propensity to trip on an obstacle.** *Gait Posture* 2007, **25:** 106-111.

7

CNS effects of indomethacin, should patients really be cautioned about decreased mental alertness and motor coordination?

Hegeman J, van den Bemt BJ, Weerdesteyn V, Nienhuis B, van Limbeek J, Duysens J: **CNS-effects of indomethacin, should patients really be cautioned about decreased mental alertness and motor coordination?** *Submitted*

Abstract

CNS (central nervous system) side effects are observed in about 5% of the patients treated with NSAIDs (non-steroidal anti-inflammatory drugs), but these effects are more common during treatment with indomethacin compared to other NSAIDs. In many European countries as well as in the USA, the leaflet or even the packaging of indomethacin contains a specific warning to refrain from activities requiring mental alertness and motor coordination, such as driving a car. In this placebo-controlled randomized study with cross-over design we attempted to find evidence for the above mentioned warning. Indomethacin 75mg slow-release or a visually identical placebo with similar flavor was taken in orally twice daily for 2.5 days. It was suggested that indomethacin affects the motor coordination required to successfully avoid obstacles during walking and that this effect will be even stronger when simultaneously performing a cognitive task puts mental alertness to the test. Nineteen healthy middle-aged individuals (60±4.7years, 8 female) were subjected to an obstacle avoidance task on a treadmill (walking velocity 3 km/hr), combined with a cognitive secondary task. Fast stepping adjustments were required to successfully avoid the obstacle, which was suddenly dropped on the treadmill. Both response times of the biceps femoris (BF, prime mover involved in avoidance reaction), measured by electromyography, and avoidance failure rates were assessed. No differences between indomethacin and placebo were found on the outcome measures regarding motor coordination, avoidance failure rates (p=0.81) and BF response times (p=0.47), nor on the performance on the secondary cognitive task (p=0.12). The present study showed that tasks which demand maximum attention remain unaffected by a high dose of indomethacin despite the frequently reported CNS side effects such as dizziness, drowsiness and headaches. A high dose of indomethacin did not affect capabilities deemed essential for safe walking in healthy senior individuals. Hence, the current study provides evidence to suggest that there might be no need to caution patients who experience CNS side effects after indomethacin use to avoid activities requiring quick and adequate reactions, such walking under challenging circumstances and maybe also driving a car.

Introduction

The prevalence of pain in the elderly is high. It is estimated that over 50% of the elderly living at home suffer from pain, a percentage which increases to 80% in long-term care patients [1,2]. When paracetamol is insufficient to reduce the pain, NSAIDs (non-steroidal anti-inflammatory drugs) are often prescribed as analgesic. As a result of that, it is estimated that over 10% of all elderly used a NSAID in the past 24 hours [3].

Although NSAIDs have proven to be effective in several inflammatory diseases, their use is often accompanied with various adverse effects such as gastrointestinal, respiratory, renal and central nervous system (CNS) problems. More specifically, these CNS problems are observed in about 5% of the patients using NSAIDs [4]. Most commonly reported problems are dizziness, headaches, drowsiness, mood alteration, and confusion [5]. The extent of CNS side effects differ between the available NSAIDs with a relatively high prevalence with indomethacin [4]. Therefore, in many European countries as well as in the USA, Competent Authorities and/or pharmaceutical companies put a specific warning in the leaflet or even on the packaging of indomethacin. This warning implies that if a user experiences CNS effects that affect physical or mental capabilities, it is discouraged to engage oneself in activities such as driving a car or operating machinery. These activities require mental alertness and motor coordination for quick and adequate responses,. However, the scientific basis for this warning remains unclear as published studies on CNS effects of indomethacin on such complex activities are ambiguous.

Tests measuring postural sway during quiet standing tasks can easily be used and serve as a moderately sensitive indicator of the CNS effects for a variety of drugs [6]. Postural balance is an important function of the CNS and is often assessed using force plates to measure vertical ground reaction forces during quiet standing. Increases in postural sway during quiet standing are usually interpreted as impaired balance control and have been determined as a reliable predictor for those at risk of falling [7]. In the latest systematic review on NSAIDs and falls it was shown that an increased risk for accidental falls is probable when elderly individuals are exposed to NSAIDs [8]. However, a recent randomized clinical trial demonstrated that a high dose of indomethacin did not affect postural sway during quiet standing in healthy senior individuals, despite the fact that 40% of the participants reported CNS side effects [9].

As a more complex activity, walking is considered to require more mental alertness and motor coordination than 'simply' keeping balance during quiet standing. Particularly, walking becomes even more complex when circumstances, such as uneven or unknown terrain or having a conversation, make it more challenging. Hence, it might be more useful to assess complex walking abilities to test for CNS side effects of NSAIDs related to falls. Obstacle avoidance during walking, for instance, is a task known to be sensitive enough to detect differences between different age groups or fallers and non-fallers [10,11]. In addition, previous research in seniors showed that divided attention [12] or even low alcohol consumption [13] significantly increased the risk of hitting an unexpected obstacle during walking due to delayed and weaker avoidance responses. For CNS effects are a well-known consequence of alcohol consumption we expected that a high dose of indomethacin could hamper obstacle avoidance skills in a similar way.

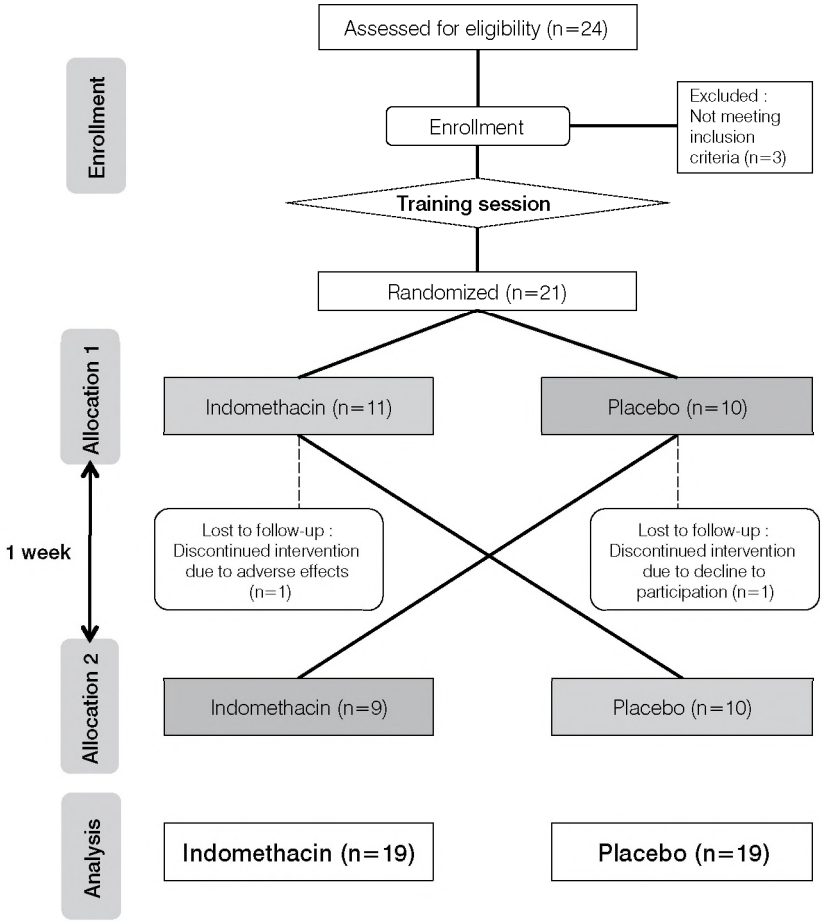
In this placebo-controlled randomized study in healthy seniors we assessed the effect of a high dose of indomethacin on mental alertness and motor coordination to find evidence for the label warning of indomethacin affecting these skills. Therefore, the present study investigated (1) whether indomethacin affects motor coordination when obstacles have to be avoided during walking, (2) whether this effect, if present, would be enhanced by the secondary cognitive task, and (3) if a high dose of indomethacin impairs the performance on the cognitive task.

Methods

Study design

A crossover design was selected for this double-blind, randomized, placebo-controlled study. Intake of indomethacin or placebo for the first measurement was randomly assigned by a pharmacist and was kept concealed until all measurements and analyses were finished. Indomethacin 75mg slow-release or a visually identical placebo with similar flavor was taken in orally twice daily. The choice for a slow-release form limited the number of capsules the participants had to take, while still reaching the desired level in the blood. The participants started their intake in the morning 2 days prior to the measurement day, taking the final capsule on the morning of the measurement, in total 5 capsules in 2.5 days. To prevent gastro-intestinal problems, all participants were given esomeprazol 20mg to be taken simultaneously with the capsule in the morning. The participants returned

Figure 1 Flowdiagram of all participants throughout the study



their empty capsule containers on the measurement day. The measurements were planned with a week interval each to completely wash out the medication.

Participants

A group of 21 healthy senior individuals (mean age 60±4.8 years, 12 male) was enrolled in this study. We included volunteers aged between 50-70 years.

Participants were excluded if they suffered from serious neurological, orthopedic or cognitive impairments, hearing problems, had poor knowledge of Dutch, or used medication that affected the locomotor system or interfered with indomethacin. All participants provided written informed consent in accordance with the Declaration of Helsinki. This study was approved by the regional ethics committee of Arnhem and Nijmegen, and the Dutch Competent Authority.

Seven participants used prescribed medication besides the study medication and were all adapted to it (Table 1). A pharmacist decided that simultaneous use of indomethacin and these medications would have no consequences for either the user or the experiment.

Table 1 Medication used by participants in the study

N = number of participants using medication from this medication class

Medication class	N	Name (ATC-code)
Proton pump inhibitors	1	Lansoprazol (A02BC03)
Blood glucose lowering drugs, excl. insulin	1	Metformin (A10BA02), tolbutamide (A10BB03)
Platelet aggregation inhibitors, excl. heparin	1	Acetylsalicylic acid (B01AC06)
Diuretics	1	Hydrochlortiazide (C03AA03)
Beta blocking agents, non-selective	2	Propanolol (C07AA05)
Beta blocking agents, selective	3	Metoprolol (C07AB02)
Selective calcium channel blockers with mainly vascular effects	2	Amlodipine (C08CA01)
ACE inhibitors, plain	2	Lisinopril (C09AA03)
Angiotensin II antagonists, plain	1	Losartan (C09CA01)
Lipid Modifying Agents, plain	3	Simvastatine (C10AA01), Atorvastatine (C10AA05)
Anti-thyroid preparations	1	Carbimazole (H03BB01)
Adrenergics and other drugs for obstructive airway diseases	1	Salmeterol/fluticason (R03AK06)

Measurements

Obstacle avoidance task

The participants were subjected to an obstacle avoidance task on a treadmill (walking velocity 3km/hr, Figure 2A, inset), wearing their own comfortable low-heeled shoes. A wooden obstacle (measuring 40x30x1.5cm) with an embedded piece of iron was held by an electromagnet just above the treadmill surface and it was released by a trigger from the computer. The obstacle was only released when a regular walking pattern (= a maximum difference of 50ms between two consecutive steps) was observed and until at least five normal strides for the trial had been completed. The obstacle was suddenly dropped on the treadmill in front of the left foot leaving only 150-550ms to react. Stepping to the side was discouraged, and any contact of the left foot with the obstacle was defined as a failure. Avoidance failure rates were assessed using visual inspection. Surface electromyography (EMG) data were collected from the m. biceps femoris (BF, a prime mover involved in the avoidance reaction [14]) to assess avoidance response times [14]. BF response times were determined as the time between obstacle release and the moment at which BF activity exceeded the average control stride activity by at least 2SDs for more than 30 ms (for example, see Figure 2A). See Hegeman et al. [13] for more details concerning the obstacle avoidance task.

Secondary cognitive task: Auditory Stroop task [15]

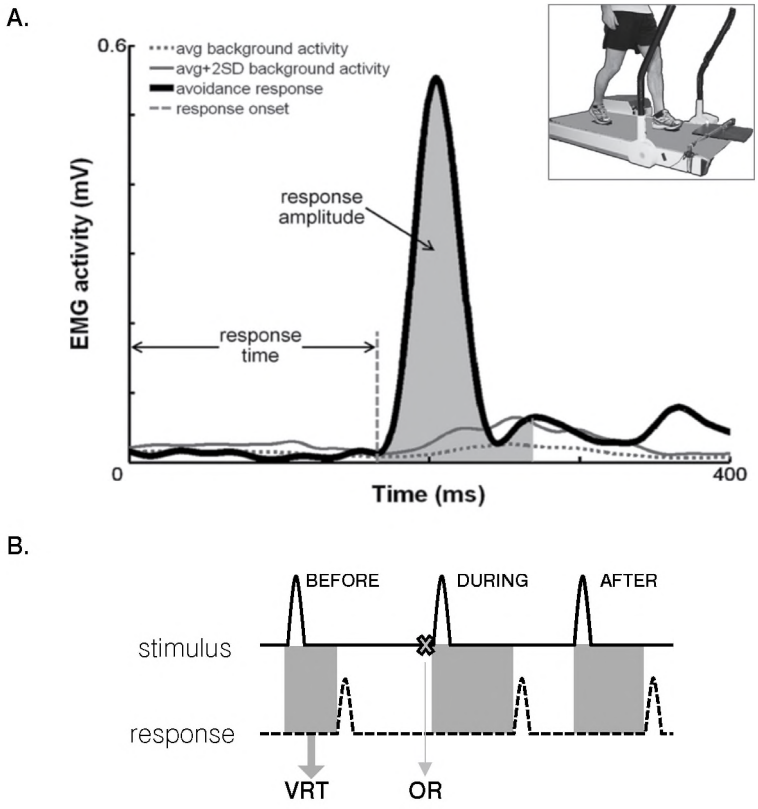
The participants listened to the words "high" or "low" in Dutch, presented in either a high or low pitch. They were instructed to indicate verbally which tone was presented as quickly as possible. The stimulus was congruent when the word and pitch matched and incongruent when they did not. Hence, incongruent stimuli were most difficult. Both stimulus and response were recorded synchronously with the data of the obstacle avoidance task.

Experimental protocol

Both the obstacle avoidance task and the cognitive task were practiced before the experiment started. Five obstacle avoidance practice trials were performed, and the auditory Stroop task was practiced until the subject felt comfortable with it while in a standing position and during walking on the treadmill. Each measurement consisted of four series of 15 obstacle avoidance trials each. All participants performed the first and fourth series of the obstacle avoidance task without cognitive task (single-task condition). The second and third series were

Figure 1 Methods

A. Determination of response of the m. biceps femoris (BF). Response time was defined as the time between obstacle release (at Time=0) and the instant where the BF activity exceeded the activity of the control stride + 2SD. Inset: experimental setup. **B**. Determination of verbal response time (VRT = time between the start of the stimulus and the start of the response) and illustration of the stimulus timings: BEFORE, DURING, and AFTER obstacle crossing. OR = obstacle release.



performed in conjunction with the auditory Stroop task (dual-task condition). Hence, each condition (single- and dual-task) comprised 30 trials. The participants were instructed not to prioritize any of the tasks, but to try their hardest to perform both tasks as well as possible.

Data analysis

For the obstacle avoidance task failure rates (the number of failed trials divided by the total number of trials) were calculated for each participant in both single- and dual-task condition of each experimental intervention. Similarly to the failure rates, average BF response times were calculated for each participant as well.

Verbal response times (VRT) on the auditory Stroop task were calculated as the time between the stimulus onset and the response. VRTs are determined by both task characteristics (congruent or incongruent stimulus) as well as the strategy used and thus speed-accuracy trade-offs have to be considered [16]. Quick verbal responses usually increase the risk of failures, whereas slower responses often improve the accuracy. Using a composite score ((100xaccuracy)/VRT) [16] takes both speed and accuracy into account. Accuracy was defined as the percentage correct responses given and when no response was given this was treated as a failure. Composite scores were calculated for the stimuli presented prior to, during and just after obstacle crossing, representing the timing of the secondary task with respect to obstacle release (OR, Figure 2B). The last stimulus and its response before obstacle release, was defined as prior to obstacle crossing. If the response was given during perturbed walking, the stimulus was defined as during obstacle crossing. The first stimulus during the recovery from avoiding the obstacle, was defined as just after obstacle crossing.

Statistical analysis

We used repeated measures ANOVAs with post-hoc pairwise comparisons (SPSS® 12.0.1: SPSS Inc., Chicago, Illinois, USA) to test for differences in obstacle avoidance outcomes (failure rates and BF response times) and in the composite scores on the secondary task. Intervention (indomethacin or placebo) was set as within-subjects factor and Sequence (start crossover with indomethacin or placebo) as between-subjects factor. For all analyses α was set at 0.05. Means for each intervention are presented with their standard errors (SE).

To calculate the sample size needed we retrieved information from previous research [13]. It was shown that the average difference in BF response times after consumption of 2 alcoholic drinks was 20ms (SD: 21ms) in a similar population [13]. To be able to identify a similar difference of 20ms in the mean BF response times between the indomethacin and placebo intervention, a sample size of 14 subjects would be needed in the present study (β= 0.9, α=0.05).

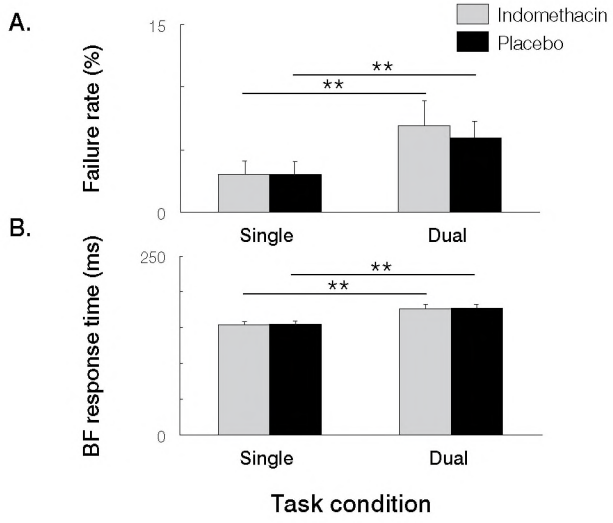
Results

Participants

Figure 1 shows a flow diagram displaying the progress of all participants through the trial. Indomethacin was randomly allocated to 11 participants for the first measurement. One participant dropped out before the first measurement because of severe nausea due to indomethacin. Another participant, assigned to placebo, declined further participation prior to the first measurement without stating a reason. Of the remaining 19 participants (60±4.7years, 11 male), 8 reported side effects when exposed to indomethacin, one of them also reported a headache when exposed to the placebo. Drowsiness (n=7), headache (n=4), and nausea (n=3) were mostly reported. The overall performance of the participants with side effects did not differ from those without reported side effects.

Figure 3 The effect of experimental intervention on **A**. the obstacle avoidance failure rate and **B**. the avoidance response times per task condition

**$p<0.01$: sign. diff. between single and dual task condition. Bars represent population mean + SE.



Obstacle avoidance task

The analysis revealed that obstacle avoidance failure rates were similar between indomethacin and placebo ($F_{1,17}$=0.06, p=0.81), both in the single- and dual-task condition ($F_{1,17}$=0.01, p=0.91). In the dual-task condition a significant doubling was revealed in failure rates (increase from 3% to 6% on average, $F_{1,17}$=12.6, p<0.01; Figure 3A), which was similar for indomethacin and placebo ($F_{1,17}$=0.15, p=0.70).

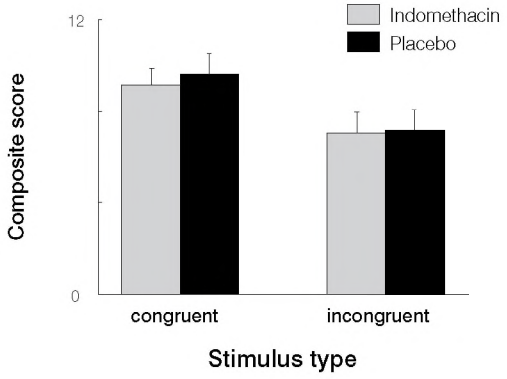
The analysis also showed that in the single- and dual-task condition ($F_{1,17}$=0.10, p=0.76) BF response times were comparable between indomethacin and placebo ($F_{1,17}$=0.55, p=0.47). For both interventions BF response times increased by 22 ms on average in the dual-task condition ($F_{1,17}$=67.4, p<0.001; Figure 3B).

Secondary task performance

The statistical analysis revealed that there were no differences between the composite scores of the indomethacin and placebo intervention ($F_{1,17}$=2.73, p=0.12; Figure 4). This similarity remained present even when the task was most difficult due to incongruent stimuli during obstacle crossing ($F_{2,16}$=1.14, p=0.35).

Figure 4 The effect of experimental condition on the secondary task performance stimulus per stimulus type

Congruent = word and pitch match, incongruent = word and pitch do not match. Bars represent population mean + SE.



Discussion

The present placebo-controlled randomized study investigated the effect of indomethacin on activities that require both motor coordination as well as mental alertness: the avoidance of suddenly appearing obstacles during walking combined with a cognitive task. The results clearly show that indomethacin had no effect on the reaction times of both the primary obstacle avoidance task and the secondary cognitive task. This finding is in line with the absence of differences in failure rates, as reaction time is an essential component of the performance. Even in the most difficult situations no differences between indomethacin and placebo were found.

To the best of our knowledge, the present study is the first to assess the effect of indomethacin on complex attention demanding tasks relevant to falls. Previous research mainly focused on psychomotor functioning [17-19]. Linnoila et al. [18] found that a single dose of 50 mg indomethacin slightly impaired performance in driving-related attention and coordination tests such as a choice reaction time test, two-coordination test and a divided attention test. On the other hand, Bruce-Jones et al. [17] and Saarialho-Kere et al. [19] showed that tests of coordination, reactive skills, attention and psychomotor speed remained unaffected after administration of indomethacin. Recent work confirmed these findings and demonstrated that neither postural balance, nor manual reaction time was affected by a high dose of indomethacin in healthy seniors [9]. In addition, the present study showed that tasks which are even more attention demanding remained unaffected by indomethacin despite the frequently reported CNS side effects such as dizziness, drowsiness and headaches.

Next to the effects of indomethacin on psychomotor functioning, previous research assessed the effects of several NSAIDs on driving performance as well [20-22]. Considering the increased risk of involvement in automobile crashes with NSAID use [20,23,24] it could be possible that CNS side effects attribute to this. However, both diclofenac and bromfenac (the latter is withdrawn due to severe side effects [25]) were found not to impair driving abilities [21,22]. In addition, McGwin et al. [24] considered it unlikely that the crash risk could be explained by the impact of NSAIDs on cognition or psychomotor performance.

The current study did not assess specific driving skills, but used a combination of tasks known to require motor coordination and mental alertness [12], and to be associated to accidental falls [10]. Similar to the knowledge that driving a car requires full concentration in order to prevent crashes, maximum concentration

was required to perform both study tasks simultaneously without hitting the obstacle. Based on the present results and our previous work [9] we therefore suggest that indomethacin is not expected to increase fall risk during walking in a senior population. Hence, the probability of an increased fall risk in elderly individuals exposed to NSAIDs demonstrated in our recent review [8] is very likely due to other (methodological) factors, such as confounding by indication.

The reported side effects after indomethacin exposure might have unblinded and thus influenced the participants. However, this seems unlikely since the performance of the participants with side effects was similar to the performance of the participants without side effects on all tasks. Moreover, the BF response times are often very fast and therefore the avoidance reaction may not be initiated consciously [14,26]. Hence, if CNS side effects were experienced by the participants it seems very unlikely that this would have affected the reaction times.

Conclusions

A high dose of indomethacin did not affect capabilities deemed essential for safe walking in healthy senior individuals. Hence, the current study provides evidence to suggest that there might be no need to caution patients who experience CNS side effects after indomethacin use to avoid activities requiring quick and adequate reactions, such as walking under challenging circumstances or even driving a car.

References

1. Ferrell BA, Ferrell BR, Rivera L: **Pain in cognitively impaired nursing home patients.** *J Pain Symptom Manage* 1995, **10:** 591-598.
2. Helme RD, Gibson SJ: **The epidemiology of pain in elderly people.** *Clin Geriatr Med* 2001, **17:** 417-31, v.
3. Demarest S, Drieskens S, Gisle L, Van der Heyden J, Tafforeau J: *Gezondheidsenquete België,2008.Rapport V - De Gezondheid van de Ouderen.* 2010.
4. Seideman P, von Arbin M: **Cerebral blood flow and indomethacin drug levels in subjects with and without central nervous side effects.** *Br J Clin Pharmacol* 1991, **31:** 429-432.
5. Weinblatt ME: **Nonsteroidal anti-inflammatory drug toxicity: increased risk in the elderly.** *Scand J Rheumatol Suppl* 1991, **91:** 9-17.
6. Swift CG: **Postural instability as a measure of sedative drug response.** *Br J Clin Pharmacol* 1984, **18 Suppl 1:** 87S-90S.
7. Lajoie Y, Gallagher SP: **Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers.** *Arch Gerontol Geriatr* 2004, **38:** 11-26.
8. Hegeman J, van den Bemt BJ, Duysens J, van Limbeek J: **NSAIDs and the risk of accidental falls in the elderly: a systematic review.** *Drug Saf* 2009, **32:** 489-498.
9. Hegeman J, Nienhuis B, van den Bemt B, Weerdesteyn V, van Limbeek J, Duysens J: **The effect of a non-steroidal anti-inflammatory drug on two important predictors for accidental falls: Postural balance and manual reaction time. A randomized, controlled pilot study.** *Hum Mov Sci* 2011, **30:** 384-395.
10. Weerdesteyn V, Nienhuis B, Duysens J: **Advancing age progressively affects obstacle avoidance skills in the elderly.** *Hum Mov Sci* 2005, **24:** 865-880.
11. Weerdesteyn V, Rijken H, Geurts AC, Smits-Engelsman BC, Mulder T, Duysens J: **A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly.** *Gerontology* 2006, **52:** 131-141.
12. Hegeman J, Weerdesteyn V, van den Bemt BJ, Nienhuis B, van Limbeek J, Duysens J: **Dual-tasking interferes with obstacle avoidance reactions in healthy seniors.** *submitted* 2011.
13. Hegeman J, Weerdesteyn V, van den Bemt BJ, Nienhuis B, van Limbeek J, Duysens J: **Even low alcohol concentrations affect obstacle avoidance reactions in healthy senior individuals.** *BMC Res Notes* 2010, **3:** 243.
14. Weerdesteyn V, Nienhuis B, Geurts AC, Duysens J: **Age-related deficits in early response characteristics of obstacle avoidance under time pressure.** *J Gerontol A Biol Sci Med Sci* 2007, **62:** 1042-1047.
15. Shor RE: **An auditory analog of the Stroop Test.** *J Gen Psychol* 1975, **93:** 281-288.
16. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM: **Dual-tasking effects on gait variability: the role of aging, falls, and executive function.** *Mov Disord* 2006, **21:** 950-957.
17. Bruce-Jones PN, Crome P, Kalra L: **Indomethacin and cognitive function in healthy elderly volunteers.** *Br J Clin Pharmacol* 1994, **38:** 45-51.
18. Linnoila M, Seppala T, Mattila MJ: **Acute effect of antipyretic analgesics, alone or in combination with alcohol, on human psychomotor skills related to driving.** *Br J Clin Pharmac* 1974, 477-484.
19. Saarialho-Kere U, Julkunen H, Mattila MJ, Seppala T: **Psychomotor performance of patients with rheumatoid arthritis: cross-over comparison of dextropropoxyphene, dextropropoxyphene plus amitriptyline, indomethacin, and placebo.** *Pharmacol Toxicol* 1988, **63:** 286-292.
20. Engeland A, Skurtveit S, Morland J: **Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study.** *Ann Epidemiol* 2007, **17:** 597-602.
21. Macdonald FC, Gough KJ, Nicoll RA, Dow RJ: **Psychomotor effects of ketorolac in comparison with buprenorphine and diclofenac.** *Br J Clin Pharmacol* 1989, **27:** 453-459.
22. Verster JC, Veldhuijzen DS, Volkerts ER: **Effects of an opioid (oxycodone/paracetamol) and an NSAID (bromfenac) on driving ability, memory functioning, psychomotor performance, pupil size, and mood.** *Clin J Pain* 2006, **22:** 499-504.
23. Foley DJ, Wallace RB, Eberhard J: **Risk factors for motor vehicle crashes among older drivers in a rural community.** *J Am Geriatr Soc* 1995, **43:** 776-781.

24. McGwin G, Jr., Sims RV, Pulley L, Roseman JM: **Relations among chronic medical conditions, medications, and automobile crashes in the elderly: a population-based case-control study.** *Am J Epidemiol* 2000, **152:** 424-431.
25. Quality Assurance and Safety of Medicines: **Regulatory Matters.** *WHO Drug Information* 1998, **12:** 146.
26. Reynolds RF, Day BL: **Visual guidance of the human foot during a step.** *J Physiol* 2005, **569:** 677-684.

8

Unravelling the association between SSRI use and falls: An experimental study on risk factors for accidental falls in long-term paroxetine users

Hegeman J, van den Bemt BJ, Weerdesteyn V, Nienhuis B, van Limbeek J, Duysens J: **Unravelling the association between SSRI use and falls: An experimental study of risk factors for accidental falls in long-term paroxetine users.** Adjusted version accepted in *Clin Neuropharmacol* 2011

Abstract

SSRIs (selective serotonin reuptake inhibitors) are widely used to treat depression and are also associated with an increased falls risk. However, the biological mechanism underlying accidental falls with SSRI intake has yet to be elucidated. The present experimental study was designed to investigate whether obstacle avoidance skills in long-term (>90 days), senior paroxetine users (61±5.8 years) are affected during gait, simple and challenging postural balance tasks, as well as during manual reaction time tasks. The performance of the paroxetine users was compared with healthy group-matched controls (60±4.8 years). The results demonstrated impaired postural balance in the paroxetine users, especially during one-legged stance or under various dual-task conditions. Although the deficit in one-legged stance could indicate vestibular involvement, this was deemed unlikely since performance of standing on compliant surface with closed eyes remained unaffected. Paroxetine use also failed to affect manual reaction times or obstacle avoidance performance. It is suggested that paroxetine affects attentional capacities particularly in conjunction with balance control. Compared to healthy seniors, senior long-term paroxetine users appear to be at an increased risk of falling due to impairments in balance control, especially when attention has to be divided between two concurrent activities.

Introduction

In 2009, 5.6% of the total Dutch population used antidepressants [1]. More than 55% of them used SSRIs (selective serotonin reuptake inhibitors); paroxetine was the most prescribed SSRI in over 40% of these users [1]. SSRIs are now widely used as a first-line treatment for depression because of their relatively mild adverse effects, particularly because of the safety in an overdose [2]. The most common side effects of SSRIs are of gastrointestinal nature: diarrhea, nausea, abdominal pain and vomiting. Less common are side effects such as headaches, hallucinations (both auditory and visual), dizziness or motion sickness, rashes and an altered sense of smell and taste. In addition, SSRIs are also associated with an increased falls risk [3] and this risk is of the same order of magnitude as that for tricyclic antidepressants (TCAs) (adjusted RR(95%CI) SSRI: 1.8(1.6-2.0), TCA: 2.0(1.8-2.2)) [4,5]. In an attempt to gain insight into the biological mechanisms underlying the increased falls risk associated with antidepressants, researchers have usually studied short-term use or single-dose effects of antidepressants on psychomotor functions or simple balance skills in young or healthy adults [6-11]. While the increased falls risk during TCA treatment is likely to be attributed to the pharmacological mode of actions of the TCAs (postural hypotension, sedation and drowsiness) [12], the biological mechanism underlying accidental falls associated with SSRI intake has not yet been elucidated. Whereas behavioral studies have failed to unravel this mechanism, epidemiological studies repeatedly have shown an increased fall risk with antidepressants primarily in older populations [3,13]. However, the possibility of confounding factors could not be completely ruled out. Hence, the need for other more specific tests and behavioral studies in an elderly population is growing. For many years researchers have developed complex balance and gait tests to assess skills more relevant to falls. Furthermore, accidental falls are found to be associated with impaired obstacle avoidance skills during walking in elderly individuals [14]. Thus far, only one study assessed the effects of antidepressants on obstructed gait in a healthy elderly group; it demonstrated that paroxetine did not affect the kinematics of stepping over obstacles during gait [15]. However, it could be that the methods used (walkway experiment with a stationary obstacle) were not sensitive enough to reveal possible subtle effects of paroxetine.

It is expected that more specific and challenging tasks with sensitive outcomes relevant to falls would be helpful to unravel the association between SSRI use and accidental falls, thereby expanding the current knowledge of this topic. Therefore the present study was designed to investigate whether paroxetine affects obstacle

avoidance skills during gait, simple and challenging postural balance tasks, and manual reaction time tasks in long-term (>90 days), senior users.

Methods

Participants

The participants in this study were community-dwelling paroxetine users and healthy controls. Participants were excluded if they suffered from serious neurological, orthopaedic or cognitive dysfunction, had poor knowledge of Dutch, or used medication other than paroxetine that affected the locomotor system. All participants gave their written informed consent in accordance with the ethical standards of the Declaration of Helsinki. The protocol was approved by the medical-ethical committee of the region Arnhem-Nijmegen.

Figure 1 Flow diagram of the participants in both the paroxetine and the control group

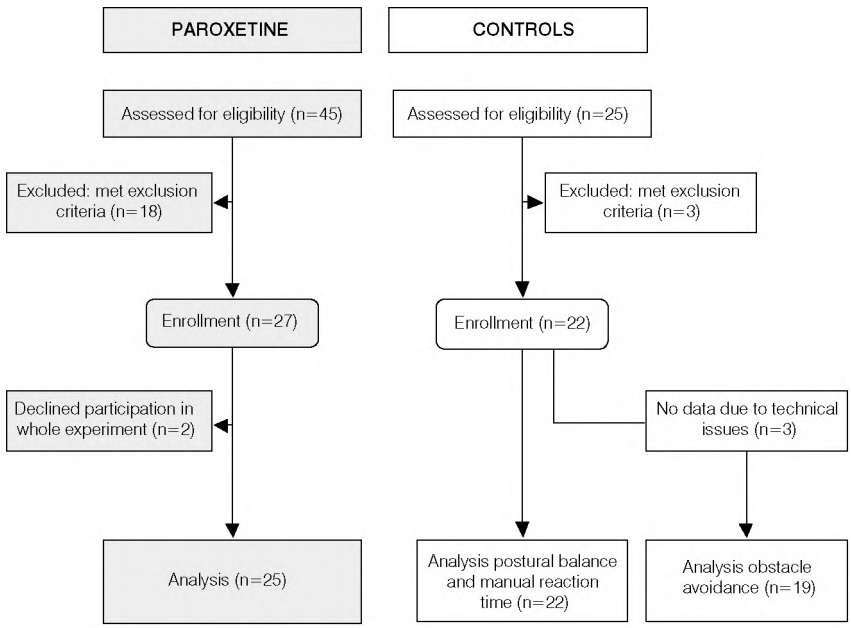


Figure 1 displays a flowchart that shows the progress of all participants during the course of the study. For the paroxetine group three regional pharmacies selected clients aged 50-70 years who had been using a maintenance dose of paroxetine for longer than 90 days. They were sent an information letter and an invitation to participate in this experiment. To indicate their interest in participation, 45 persons sent a reply card to the researcher. A questionnaire with items on medication use, health status and physical activity was used to assess eligibility for participation in the study. Of these 45 persons, eighteen were judged to be ineligible (neurological impairments (n=2); musculoskeletal problems (n=7), poor knowledge of Dutch (n=1), age (n=2), and use of medication that affected the CNS or locomotor system (n=6)). Another two individuals declined participation without reason. The remaining 25 paroxetine users (mean age 61±5.8 years; 13 male, Table 1) performed the whole experiment.

Table 1 Baseline characteristics of the study groups

	Paroxetine	Controls	*p*-value
Gender (M:F)	13:12	12:10	-
Age (yrs)	61 (5.8)	60 (4.8)	0.32
Height (cm)	172 (11)	169 (8)	0.43
Weight (kgs)	80 (13)	74 (12)	0.13
BMI	27 (2.4)	26 (3.4)	0.18

Twenty-five group-matched for age controls were recruited from several regional hobby clubs. Therefore these controls were inhabitants of the same region as the paroxetine users. After assessment for eligibility 22 persons (mean age 60±4.8; 12 male, Table 1) were enrolled; three persons were excluded due to musculoskeletal problems (n=1) or use of medication that affected the CNS or locomotor system (n=2). All 22 controls performed the set of postural balance tasks and the manual reaction time task. Data from 19 who persons performed the obstacle avoidance task was obtained as data for three participants could not be obtained due to technical malfunctioning during the task.

Ten paroxetine users and seven controls used other prescribed medication to which they were well accustomed. A list of medication used by these participants is presented in Table 2. A pharmacist determined that none of these medications were considered to independently affect the CNS or to lead to problems of any kind with regard to the experiment.

Table 2 Medication used by participants in the study

C=control group, P=paroxetine group
N=number of participants using medication from this medication class.

Medication class		N	Name (ATC-code)
Proton pump inhibitors	C	1	Lansoprazol (A02BC03)
	P	**1**	**Pantoprozol (A02BC02)**
Blood glucose lowering drugs, excl. insulin	C	1	Metformin (A10BA02), tolbutamide (A10BB03)
	P	**2**	**Metformin (A10BA02), tolbutamide (A10BB03)**
Platelet aggregation inhibitors, excl. heparin	C	1	Acetylsalicylic acid (B01AC06)
	P	**2**	**Clopidogrel (B01AC04), Acetylsalicylic acid (B01AC06), carbasalate calcium (B01AC08)**
Diuretics	C	1	Hydrochlortiazide (C03AA03)
	P	**3**	**Hydrochlortiazide (C03AA03), Chlortalidon (C03BA04)**
Beta blocking agents, non-selective	C	2	Propanolol (C07AA05)
Beta blocking agents, selective	C	3	Metoprolol (C07AB02)
Selective calcium channel blockers with mainly vascular effects	C	2	Amlodipine (C08CA01)
ACE inhibitors, plain	C	2	Lisinopril (C09AA03)
	P	**2**	**Fosinopril (C09AA09)**
Angiotensin II antagonists, plain	C	1	Losartan (C09CA01)
Lipid Modifying Agents, plain	C	3	Simvastatine (C10AA01), Atorvastatine (C10AA05)
	P	**8**	**Simvastatine (C10AA01), Pravastatin (C10AA03), Atorvastatine (C10AA05)**
Progestogens and estrogens, fixed combinations	**P**	**1**	**Lynestrenol and estrogen (G03AA03)**
Anti-thyroid preparations	C	1	Carbimazole (H03BB01)
Enzyme inhibitors	**P**	**1**	**Anastrozole (L02BG03)**
Adrenergics and other drugs for obstructive airway diseases	C	1	Salmeterol/fluticason (R03AK06)

Study protocol

Each participant performed three tasks which assessed manual reaction time, postural balance, and obstacle avoidance skills. The tasks are briefly described below; for more details see Hegeman et al. [16,17]. Task sequence was randomized between the participants. To eliminate possible learning effects, all tasks were practiced prior to the actual measurement. The paroxetine users also completed the Hospital Anxiety and Depression Scale (HADS) [18] to assess the degree of anxiety and depression.

Equipment and procedure

Manual reaction time tasks

A button box with a home button and five target buttons was used to perform simple (15 trials, 1 target button) and choice (45 trials, 3 target buttons, more difficult) reaction time tasks (Figure 2A). Always starting from the home button, participants had to press the target button as quickly as possible after its illumination. If they reacted too fast (<150ms), too slow (>1000ms) or failed to press the target button, the trial was repeated at the end of the sequence. Both tasks were performed twice; the second recording occurred in reversed order to counterbalance fatigue effects. Reaction time (time between illumination of the target button and release of the home button) was recorded in milliseconds and median reaction times were included in the statistical analysis of both reaction time tasks.

Balance tasks

Postural balance was assessed using a firmly secured custom-made force platform consisting of two separate aluminum plates, each placed on three force transducers that recorded the vertical ground reaction forces. The participants stood barefoot on the force platform with their feet against a fixed foot frame and their arms hanging alongside the trunk (Figure 2B). Participants were instructed to stand as still as possible while performing a set of 9 balance tasks (5 as a single task, with 4 also under dual-task conditions). Before the balance measurements started, the dual-task condition with the cognitive task (an auditory Stroop task [19]) was practiced without paying attention to balance until the participant felt comfortable with it. This cognitive task required participants to listen to the words “high” or “low” in Dutch, presented in either a high or low pitch and to verbally indicate the tone as soon as possible (at most 18 times per balance task).

The balance tasks in the single-task condition consisted of quiet stance on both legs either with eyes open (firm or compliant surface) and eyes closed (firm or compliant surface), and stance on one leg (the preferred one on the firm surface). In the dual-task condition these tasks, except for stance on both legs on compliant surface with eyes closed, were repeated with a secondary cognitive task.

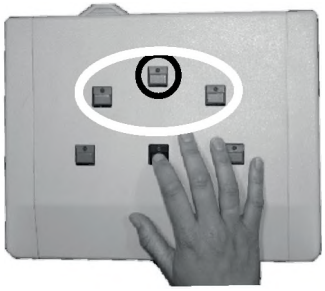
The Root Mean Square (RMS) of the centre of pressure (COP, Figure 2B) velocity was selected as the outcome measure since it has been shown to be the most reliable [20,21]. In the quantification of postural balance higher RMS values of this variable indicate poorer performance. RMS values of COP velocity in the anterior-posterior direction were computed for all tasks. For one-legged stance, the RMS COP velocity was also computed in the lateral direction as lateral stability plays a major role in one-legged stance. Each of the balance tasks was performed twice; the second recording with the sequence in reversed order to exclude the influence of fatigue. For every task, the mean RMS value was included in the statistical analysis.

Obstacle avoidance task

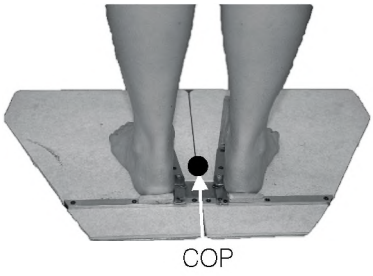
The participants performed an obstacle avoidance task on a treadmill (walking velocity 3km/hr; Figure 2C, inset), wearing their own comfortable low-heeled shoes and a safety harness. A wooden obstacle (measuring 40x30x1.5cm) with an embedded piece of iron, held by an electromagnet just above the treadmill surface was released by a trigger from the computer. A regular walking pattern was needed and at least five unperturbed strides had to be completed before the obstacle was released. Fast stepping adjustments were required to successfully avoid the obstacle which was suddenly dropped on the treadmill in front of the left foot leaving at most 550ms to react. Contact of the left foot with the obstacle or stepping to the side was defined as a failure. Failures were noted during the experiment and failure rates (the number of failed trials divided by the total number of trials) were calculated for each participant. In addition, surface electromyography (EMG) data were collected from the m. biceps femoris (BF, a prime mover involved in the avoidance reaction [22]) to assess avoidance response times. BF response times were determined as the time between obstacle release and the moment at which BF activity exceeded the average control stride activity by at least 2SDs for more than 30 ms (for an example, see Figure 2C).

Figure 2 Experimental setup. **A**. Manual reaction time tasks (simple: one target button (black circle), choice: 3 target buttons (white circle). **B**. Force platform for static balance tasks (COP= Center of Pressure). **C**. Obstacle avoidance task.

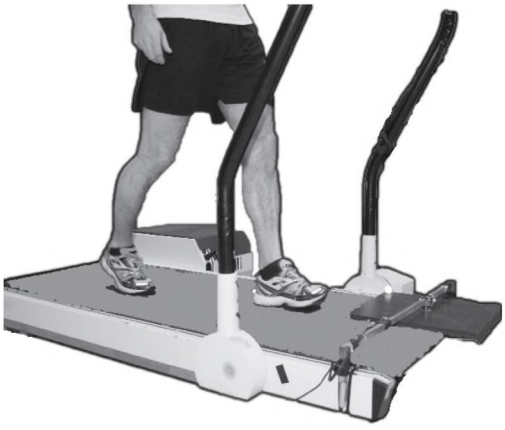
A.



B.



C.



Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-item, self-report screening scale that was originally developed to indicate the possible presence of anxiety and depressive states in the setting of a medical out-patient clinic [18]. In the present study a validated Dutch version of the HADS [23] was used to assess the degree of anxiety and depression in the paroxetine group. As we did not obtain HADS scores from the control group, the HADS scores of the paroxetine users were compared with the scores from a random sample of Dutch senior individuals taken from the general population (n=1901; mean age±SD: 61±2.3yrs) [23].

Statistical analysis

Independent t-tests were carried out in SPSS® (version 12.0.1) to assess differences between long-term paroxetine users and the age-matched healthy controls on population characteristics, manual reaction time, and postural balance as well as obstacle avoidance skills. The level of significance was set at 0.05, and a post-hoc Bonferroni correction was applied. Means are presented with their SE (standard error).

To calculate the sample size needed for this study, we used information from a previous study [17]. That study indicated that a relevant average difference in the RMS COP velocity during one-legged stance was 10mm/s (SD: 9mm/s) in a similar population. To be able to identify a difference of 10mm/s in this outcome measure, one needs to study at least 18 paroxetine users and 18 controls (β= 0.9, α=0.05).

Results

Participants

Independent t-tests showed that the average height, weight and Body Mass Index for both groups in this study were comparable (p>0.10, Table 1). The paroxetine group used on average 22mg±4 paroxetine daily and the duration of use was 6.6±0.8 years (self-reported).

Manual reaction time

The analysis revealed that paroxetine users and controls responded equally fast on the simple reaction time task (paroxetine: 261ms±6.8 vs. controls: 260ms±6.4;

p=0.90) as well as the choice reaction time task (268ms±7.0 vs. 279ms±6.6; p=0.26; Table 3).

Table 3 Results of the experimental tasks (mean±SE)

Bold numbers indicate a significant differences between the paroxetine group and the control group (after post-hoc Bonferroni correction α=0.008)

Task	Paroxetine	Controls	*p*-value
Obstacle avoidance			
Failure rate (%)	8.5 (1.5)	7.3 (1.7)	0.45
Response time (ms)	164 (2.8)	161 (4.4)	0.46
Manual reaction time			
Simple task (ms)	261 (6.8)	260 (6.4)	0.90
Choice task (ms)	268 (7.0)	279 (6.6)	0.26
Postural balance			
One leg, firm suface, AP			
Single task (mm/s)	36 (1.9)	24 (2.0)	**<0.001**
Dual task (mm/s)	92 (11)	43 (12)	**0.003**
One leg, firm suface, LAT			
Single task (mm/s)	45 (1.9)	36 (2.0)	**0.001**
Dual task (mm/s)	87 (11)	49 (12)	**0.001**
Two legs, firm surface			
Eyes open, single task (mm/s)	8.0 (0.38)	7.4 (0.41)	0.25
Eyes open, dual task (mm/s)	11 (0.62)	8.4 (0.65)	0.01
Eyes closed, single task (mm/s)	14 (0.86)	12 (0.91)	0.16
Eyes closed, dual task (mm/s)	15 (0.99)	14 (1.1)	0.36
Two legs, compliant surface			
Eyes open, single task (mm/s)	15 (0.73)	13 (0.77)	0.08
Eyes open, dual task (mm/s)	19 (0.75)	15 (0.80)	**0.001**
Eyes closed (mm/s)	40 (2.4)	38 (2.5)	0.73

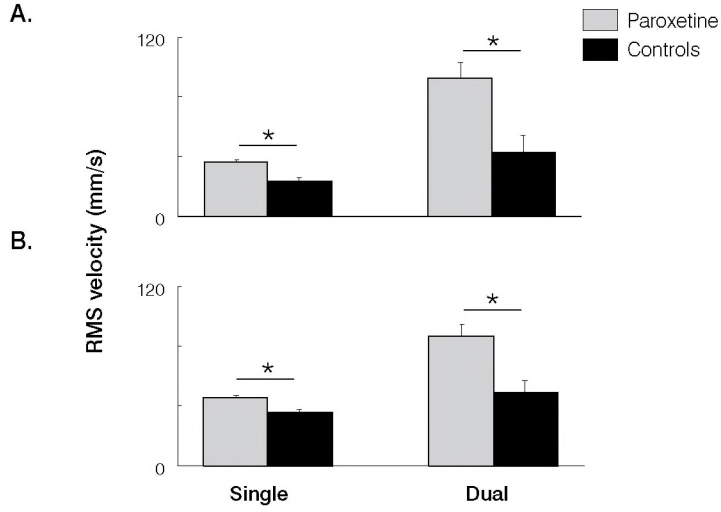
Postural balance

The analysis showed that paroxetine users had significantly higher RMS COP velocities than the control group on the one-legged stance task both in the single-

and the dual task conditions (Table 3). Figure 3 presents the average RMS COP velocity of the one-legged stance task in the anterior-posterior (A) and lateral (B) direction and clearly shows that in both directions the paroxetine users had significantly higher COP velocities than the controls. Moreover, under dual task conditions in the one-legged stance task, the COP velocities of the paroxetine users were about twice as fast as those of the control group (92mm/s±11 vs. 43m/s±12 (p=0.003) for the anterior-posterior direction and 87mm/s±8 vs. 49mm/s±8 (p=0.001) for the lateral direction). Table 3 also shows that paroxetine users had significantly higher RMS COP velocities than the control group on two other balance tasks (quiet stance on both legs with eyes open on the firm and the compliant surface) performed under dual-task conditions (firm surface: 11mm/s±0.6 vs. 8.4 mm/s±0.7 (p=0.01); compliant surface: 19mm/s±0.8 vs. 15mm/s±0.8 (p=0.001)).

Figure 3 The effect of paroxetine use on one-legged stance under single- and dual-task conditions

A. anterior-posterior direction, **B**. lateral direction. * $p<0.01$ significant difference between paroxetine users and healthy age-matched controls (after post-hoc Bonferroni correction α=0.008). Bars represent population mean + SE.



Obstacle avoidance

Independent t-tests revealed that the avoidance failure rates of the paroxetine users were similar to the rates of the control group (paroxetine: 8.5%±1.5 vs. controls: 7.3%±1.7; $p=0.45$; Table 3). The latencies of the avoidance responses of the paroxetine users were also comparable to those of the controls (164ms±2.8 vs. 161ms±4.4; $p=0.46$; Table 3).

Hospital Anxiety and Depression Scale (HADS)

Paroxetine users had a significantly higher total score on the HADS than the published comparison group (average (±SD): 11±5.9 versus 7.6±6.0, $p<0.001$). Paroxetine users appeared to be more anxious (7.0±3.1 vs. 3.9±3.5, $p<0.001$), but not more depressed than the comparison group (4.2±3.7 vs. 3.7±3.3, $p=0.45$). For it is known that anxiety could affect postural balance [24-26] we assessed whether the anxiety scores of the paroxetine users were correlated to their postural balance performance. Therefore we used the performance on the one-legged stance task under single-task conditions on which the clearest difference between paroxetine users and controls was found. For the paroxetine users of the present study, anxiety was not correlated to postural balance (COP velocity anterior-posterior 36mm/s±1.9, $r=0.01$, $p=0.95$; lateral direction 45mm/s±1.9, $r=0.12$, $p=0.58$).

Discussion

To the best of our knowledge this is the first study to investigate the effect of long-term paroxetine use on an extensive set of tasks relevant to falls. Previous research on this topic might have been not sensitive enough, which probably explains why the current body of knowledge is limited. The present study was designed to extend the knowledge of the association between SSRI use and accidental falls. A comparison was made between the performance of long-term paroxetine users and age-matched controls on manual reaction time tasks, challenging postural balance tasks, and a time-critical obstacle avoidance task during gait. The results demonstrated impaired postural balance with paroxetine use, especially during one-legged stance or under dual-task conditions. In contrast, paroxetine use did not affect either manual reaction times or obstacle avoidance performance.

Postural balance

Earlier research mainly focused on the effect of treatment with paroxetine on stance with either eyes open or eyes closed in the depressed elderly [8,27]. These studies found no differences in postural sway parameters after 6 weeks of paroxetine use [8,27]. In contrast, the present results showed in the paroxetine group an increase in postural sway on all balance tasks, though it was only significant during one-legged stance and when a concurrent cognitive task was performed. It is known that impaired balance [28] and unipedal stance time shorter than 30 seconds [29] are important predictors for fall risk in older people. Moreover, many researchers have demonstrated that attention division has detrimental effects on postural balance (for a review see Woollacott & Shumway-Cook [30]). In turn these balance deficits are associated to accidental falls [31,32]. This could imply that our paroxetine group was at a greater risk of falling.

Manual reaction time

Previous research showed no effect of paroxetine (20mg) on manual reaction time [33-35]. Even though some essential differences between these studies and the present study exist, the findings are in line with our results. Having taken into account the variation in both the age groups and the durations of paroxetine use, we expect paroxetine not to affect manual reaction times in general.

Obstacle avoidance

To date only one study has investigated the effects of a single doses of antidepressants on obstructed and unobstructed gait; it did not affect the performance on these tasks [15]. Despite the increased difficulty level and long-term paroxetine use, the results of the present study are in line with those of Draganich et al. [15] for we found no effect of paroxetine on both failure rates and avoidance reaction times. Earlier research demonstrated that an increased difficulty level is successful in assessing of obstacle avoidance skills [14,16,36]. Hence, the present paradigm (obstacle avoidance under time pressure) could serve as a more sensitive tool to assess the effect of paroxetine on obstacle avoidance during gait. Nevertheless, for the present group the conclusions remain similar to those found with less challenging conditions. Indeed paroxetine was found not to have deleterious effects on gait and obstacle avoidance skills. Hence, it is suggested to be safe to use in elderly patients with regard to gait [15].

However, the question arises why we see only some clear differences on the static balance tasks while the performance on the manual reaction time and obstacle avoidance tasks remained unaffected by paroxetine. One potential indication is the fact that dizziness is the most frequently reported symptom of abrupt discontinuation of treatment with paroxetine [37,38]. Dizziness after withdrawal is more common for SSRIs with a much higher selectivity for serotonin than for noradrenaline [39]. Paroxetine is one of the most selective and effective SSRIs in blocking the reuptake of serotonin. This suggests that the effects of the serotonergic systems in the CNS are expected to be the main cause of such dizziness [39], besides the effects of the histaminergic and dopaminergic system. The involvement of serotonin on the vestibular system is implied by the finding that this dizziness is likely to be vestibular in origin for slight movements of the head often have an intensifying effect [40]. The finding that paroxetine can be effective in the treatment of some kinds of dizziness [41] since the presence of serotonin in the vestibular nuclei affects motion sensitive neural pathways [42,43] also implies involvement of serotonin on the vestibular system.

However, the results of the present study do not support the suggestion that it is primarily the vestibular system that is involved since paroxetine did not affect quiet standing on the compliant surface with the eyes closed. During this task both the proprioceptive and the visual systems – of which the input is important with regard to balance control – were limited and balance control mainly relied on the vestibular system. In addition, the increases in postural sway during the dual-task conditions are not likely to be due to changes in vestibular functioning. It has been shown that the ability to maintain static balance involves additional attentional demands [30,44]. Moreover, age differences in balance abilities are known to be magnified by a secondary cognitive task [31,32]. Hence, these results seem to indicate that paroxetine affects attentional capacities and thereby affects balance abilities. However, clear evidence on the effects of paroxetine on human attention is lacking and future research is needed to elucidate the role of attention in falls after paroxetine use.

It may be argued that the present results reflect the presence of depression more than of the use of paroxetine. Indeed it is well-known that anxiety or depression could affect postural balance [24-26] and are both risk factors for falls [45]. However, in the present study we found no correlation between the HADS scores and postural sway in the paroxetine group. Therefore, it seems unlikely that the effect of anxiety or depression on balance control could explain the increases in postural sway found in this group. An additional question is

whether the augmented sway is an acceptable risk. Darowski et al. [12] suggested that the magnitude of the increased risk of falling associated with an antidepressant is about the same as the excess risk found in patients with untreated depression. Despite their treatment the paroxetine users in the present study appear to be at an increased risk of falling since impaired balance control itself is a risk factor for falls [46]. However, this increased risk probably does not exceed the increased risk that the same patients would run if they had not taken paroxetine.

A limitation of the present study is that we did not obtain HADS scores of the control group and hence, we could not assess anxiety or depression in that group. Nevertheless, we feel confident that the data of a similar age group from a previous validation study [23] served as an appropriate alternative for the comparison with the paroxetine users since this control group was well-matched and consisted of a representative sample of the elderly population.

The question arises whether the present results can be generalized to all antidepressants in the SSRI category since we assessed only paroxetine users. Future research should expand on this new knowledge by including other SSRIs to further unravel the association between SSRI use and falls.

Conclusions

In conclusion, compared to healthy seniors, senior long-term paroxetine users appear to be at an increased risk of falling due to impairments in balance control, especially when attention has to be divided between two concurrent activities. However, additional research is needed to further unravel the biological mechanism underlying accidental falls after SSRI intake.

References

1. www.gipdatabank.nl. 2011.
2. Vaswani M, Linda FK, Ramesh S: **Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review.** *Prog Neuropsychopharmacol Biol Psychiatry* 2003, **27:** 85-102.
3. Kerse N, Flicker L, Pfaff JJ, Draper B, Lautenschlager NT, Sim M *et al.*: **Falls, depression and antidepressants in later life: a large primary care appraisal.** *PLoS One* 2008, **3:** e2423.
4. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N: **Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people.** *Lancet* 1998, **351:** 1303-1307.
5. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA: **Antidepressants and the risk of falls among nursing home residents.** *N Engl J Med* 1998, **339:** 875-882.
6. Paleacu D, Shutzman A, Giladi N, Herman T, Simon ES, Hausdorff JM: **Effects of pharmacological therapy on gait and cognitive function in depressed patients.** *Clin Neuropharmacol* 2007, **30:** 63-71.
7. Hawley CJ, McPhee S, Quick SJ, Smith VR: **A review of the psychomotor effects of paroxetine.** *Int Clin Psychopharmacol* 1997, **12:** 13-18.
8. Mamo DC, Pollock BG, Mulsant B, Houck PR, Bensasi S, Miller MC *et al.*: **Effects of nortriptyline and paroxetine on postural sway in depressed elderly patients.** *Am J Geriatr Psychiatry* 2002, **10:** 199-205.
9. Paul MA, Gray GW, Love RJ, Lange M: **SSRI effects on pyschomotor performance: assessment of citalopram and escitalopram on normal subjects.** *Aviat Space Environ Med* 2007, **78:** 693-697.
10. Li X, Hamdy R, Sandborn W, Chi D, Dyer A: **Long-term effects of antidepressants on balance, equilibrium, and postural reflexes.** *Psychiatry Res* 1996, **63:** 191-196.
11. Hasbroucq T, Rihet P, Blin O, Possamai CA: **Serotonin and human information processing: fluvoxamine can improve reaction time performance.** *Neurosci Lett* 1997, **229:** 204-208.
12. Darowski A, Chambers SA, Chambers DJ: **Antidepressants and falls in the elderly.** *Drugs Aging* 2009, **26:** 381-394.
13. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC *et al.*: **Central nervous system-active medications and risk for falls in older women.** *J Am Geriatr Soc* 2002, **50:** 1629-1637.
14. Weerdesteyn V, Nienhuis B, Duysens J: **Advancing age progressively affects obstacle avoidance skills in the elderly.** *Hum Mov Sci* 2005, **24:** 865-880.
15. Draganich LF, Zacny J, Klafta J, Karrison T: **The effects of antidepressants on obstructed and unobstructed gait in healthy elderly people.** *J Gerontol A Biol Sci Med Sci* 2001, **56:** M36-M41.
16. Hegeman J, Weerdesteyn V, van den Bemt BJ, Nienhuis B, van Limbeek J, Duysens J: **Even low alcohol concentrations affect obstacle avoidance reactions in healthy senior individuals.** *BMC Res Notes* 2010, **3:** 243.
17. Hegeman J, Nienhuis B, van den Bemt B, Weerdesteyn V, van Limbeek J, Duysens J: **The effect of a non-steroidal anti-inflammatory drug on two important predictors for accidental falls: Postural balance and manual reaction time. A randomized, controlled pilot study.** *Hum Mov Sci* 2011, **30:** 384-395.
18. Zigmond AS, Snaith RP: **The hospital anxiety and depression scale.** *Acta Psychiatr Scand* 1983, **67:** 361-370.
19. Shor RE: **An auditory analog of the Stroop Test.** *J Gen Psychol* 1975, **93:** 281-288.
20. Geurts AC, Nienhuis B, Mulder TW: **Intrasubject variability of selected force-platform parameters in the quantification of postural control.** *Arch Phys Med Rehabil* 1993, **74:** 1144-1150.
21. Lafond D, Duarte M, Prince F: **Comparison of three methods to estimate the center of mass during balance assessment.** *J Biomech* 2004, **37:** 1421-1426.
22. Weerdesteyn V, Nienhuis B, Geurts AC, Duysens J: **Age-related deficits in early response characteristics of obstacle avoidance under time pressure.** *J Gerontol A Biol Sci Med Sci* 2007, **62:** 1042-1047.

23. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM: **A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects.** *Psychol Med* 1997, **27:** 363-370.
24. Kose N, Cuvalci S, Ekici G, Otman AS, Karakaya MG: **The risk factors of fall and their correlation with balance, depression, cognitive impairment and mobility skills in elderly nursing home residents.** *Saudi Med J* 2005, **26:** 978-981.
25. Wada M, Sunaga N, Nagai M: **Anxiety affects the postural sway of the antero-posterior axis in college students.** *Neurosci Lett* 2001, **302:** 157-159.
26. Balaban CD: **Neural substrates linking balance control and anxiety.** *Physiol Behav* 2002, **77:** 469-475.
27. Laghrissi-Thode F, Pollock BG, Miller MC, Mulsant BH, Altieri L, Finkel MS: **Double-blind comparison of paroxetine and nortriptyline on the postural stability of late-life depressed patients.** *Psychopharmacol Bull* 1995, **31:** 659-663.
28. Rubenstein LZ: **Falls in older people: epidemiology, risk factors and strategies for prevention.** *Age Ageing* 2006, **35 Suppl 2:** ii37-ii41.
29. Hurvitz EA, Richardson JK, Werner RA, Ruhl AM, Dixon MR: **Unipedal stance testing as an indicator of fall risk among older outpatients.** *Arch Phys Med Rehabil* 2000, **81:** 587-591.
30. Woollacott M, Shumway-Cook A: **Attention and the control of posture and gait: a review of an emerging area of research.** *Gait Posture* 2002, **16:** 1-14.
31. Maylor EA, Wing AM: **Age differences in postural stability are increased by additional cognitive demands.** *J Gerontol B Psychol Sci Soc Sci* 1996, **51:** 143-154.
32. Shumway-Cook A, Woollacott M, Kerns KA, Baldwin M: **The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls.** *J Gerontol A Biol Sci Med Sci* 1997, **52:** M232-M240.
33. Ridout F, Meadows R, Johnsen S, Hindmarch I: **A placebo controlled investigation into the effects of paroxetine and mirtazapine on measures related to car driving performance.** *Hum Psychopharmacol* 2003, **18:** 261-269.
34. Kerr JS, Fairweather DB, Mahendran R, Hindmarch I: **The effects of paroxetine, alone and in combination with alcohol on psychomotor performance and cognitive function in the elderly.** *Int Clin Psychopharmacol* 1992, **7:** 101-108.
35. De Bruijn ER, Sabbe BG, Hulstijn W, Ruigt GS, Verkes RJ: **Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers.** *Brain Res* 2006, **1105:** 122-129.
36. Hofstad CJ, Weerdesteyn V, van der Linden H, Nienhuis B, Geurts AC, Duysens J: **Evidence for bilaterally delayed and decreased obstacle avoidance responses while walking with a lower limb prosthesis.** *Clin Neurophysiol* 2009, **120:** 1009-1015.
37. Dominguez RA, Goodnick PJ: **Adverse events after the abrupt discontinuation of paroxetine.** *Pharmacotherapy* 1995, **15:** 778-780.
38. Himei A, Okamura T: **Discontinuation syndrome associated with paroxetine in depressed patients: a retrospective analysis of factors involved in the occurrence of the syndrome.** *CNS Drugs* 2006, **20:** 665-672.
39. Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH *et al.*: **Possible biological mechanisms of the serotonin reuptake inhibitor discontinuation syndrome. Discontinuation Consensus Panel.** *J Clin Psychiatry* 1997, **58 Suppl 7:** 23-27.
40. Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH *et al.*: **Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. Discontinuation Consensus panel.** *J Clin Psychiatry* 1997, **58 Suppl 7:** 5-10.
41. Horii A, Mitani K, Kitahara T, Uno A, Takeda N, Kubo T: **Paroxetine, a selective serotonin reuptake inhibitor, reduces depressive symptoms and subjective handicaps in patients with dizziness.** *Otol Neurotol* 2004, **25:** 536-543.
42. Li VG, Licata F, Fretto G, Mauro MD, Santangelo F: **Influence of serotonin on the glutamate-induced excitations of secondary vestibular neurons in the rat.** *Exp Neurol* 2001, **172:** 446-459.
43. Sugihara I, Lang EJ, Llinas R: **Serotonin modulation of inferior olivary oscillations and synchronicity: a multiple-electrode study in the rat cerebellum.** *Eur J Neurosci* 1995, **7:** 521-534.

44. Lajoie Y, Teasdale N, Bard C, Fleury M: **Attentional demands for static and dynamic equilibrium.** *Exp Brain Res* 1993, **97:** 139-144.
45. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS: **Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group.** *Arch Intern Med* 1999, **159:** 484-490.
46. Lajoie Y, Gallagher SP: **Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers.** *Arch Gerontol Geriatr* 2004, **38:** 11-26.

9

General discussion

General discussion

The purpose of this thesis was to gain insight into the extent to which medication could affect fall-related skills. The knowledge gained could lead to a reduction in medication-related accidental falls. Therefore, this thesis consisted of two parts. The first part dealt with the composition of a set of tasks to assess fall-related skills. More specifically, the aim was to investigate new sensitive tasks in assessing of the effect of medication on these skills. Thereupon, in the second part these tasks were added to existing conventional tasks to assess fall risk factors in two medication groups frequently prescribed to seniors and suspected to increase fall risk in users of such medication.

In this general discussion the main findings and conclusions of the studies described in the chapters of the two parts of this thesis are further discussed and recommendations for future research are given.

New tasks for the assessment of the effect of medication on fall-related skills

By means of three separate studies the first part of this thesis provides a basis for the use of a time-critical obstacle avoidance task and a secondary cognitive task to assess the effects of medication on skills related to accidental falls. Poor performance levels either on obstacle avoidance [1] or on dual-task walking [2] were previously shown to be associated with an increased risk of falling.

Previous research has demonstrated that a time-critical obstacle avoidance task can reveal differences in obstacle avoidance skills between young adults and elderly as well as fallers and non-fallers [1,3,4]. However, it was unknown whether such a task would be sensitive enough to reveal possible effects of chemical substances such as medication. Alcohol is a substance well-known to affect CNS functions such as gait. Therefore we considered alcohol as a "gold standard" and assessed the effects of alcohol on obstacle avoidance skills during gait in healthy senior individuals (mean age (±SD) 62±4.4 years). We concluded that even low alcohol consumption was detrimental to these fall-related skills. This was most prominent in difficult situations where time pressure was high. In these situations fast reactions are required to successfully avoid the obstacle. It was suggested that the fast supraspinal pathways supposedly involved in these avoidance reactions were altered by the consumption of alcohol. Hence, the

results of that study served as a 'proof-of-principle' and we concluded that a time-critical obstacle avoidance task was sensitive to assess CNS (side) effects of medication.

As another skill related to accidental falls, dual-task walking has been extensively studied (for a review see Woollacott & Shumway-Cook [5] and Yogev et al. [6]). However, the interpretation of many studies using a dual-task paradigm in conjunction with gait leaves room for speculation as to what extent attention division has actually occurred. To clarify this issue, both the primary gait task and the cognitive secondary task should be attentionally demanding and the instruction should be not to prioritize either one of the tasks. By doing so, optimal performance on both tasks will be needed when performed simultaneously and the contribution of either one of the tasks on dual-task interference might be revealed. Therefore, two studies of this thesis investigated the effect of dual-tasking on commonly encountered difficulties in gait, such as limping and avoiding sudden obstacles. To minimize potentially conflicting sensory modalities during gait, we chose to use a secondary task not related to vision or locomotion and difficult enough to load the attentional system: the auditory Stroop task [7]. We demonstrated in healthy young adults (26±3.8 years) that this auditory task was useful to detect how small changes in gait occur when limping causes gait to be less automatic. It was shown that dual-tasking during asymmetric walking significantly affected the primary gait task whereas the secondary cognitive task remained practically unchanged. Given these findings, a 'posture second' strategy could be the case in this study, implying that mainly motor functions are affected under dual-task conditions. However, it remained unclear if, and to what extent, mental alertness - another important CNS function - was actually called upon. Therefore, we performed another study to increase our insight in dual-task interference using sensitive outcome measures for both the primary and secondary task. In addition, we investigated whether such a 'posture second' strategy could also be the case when suddenly appearing obstacles have to be avoided during gait under dual-task conditions. Deteriorated obstacle avoidance reactions were found as well as decreased performance on the secondary cognitive task. This was considered an indication for limited capacity of CNS functions and the suggestion of a 'posture second' strategy was rejected for this particular task. Hence, the methods used proved to be sensitive enough to reveal clear dual-task interference on both tasks. Considering these findings, we concluded that the dual-task paradigm of a time-critical obstacle avoidance task combined with an auditory secondary task can be a useful method to investigate CNS adverse effects of medication.

The assessment of fall risk factors in medication users

Both age-induced changes to the locomotor apparatus as well as medication use are found to be related to accidental falls in the elderly [8-13]. Several tests, such as quiet stance tasks and obstacle avoidance tasks have been developed to investigate the effects of these age-induced changes [14-16] and are expected to be suitable to assess the CNS adverse effects of medication as well. On the other hand, most studies on the relation between medication use and falls were of epidemiological nature. It was shown that primarily psycho-active medication, analgesics, diuretics, and vasodilators are associated with an increased fall risk [9,17-20]. However, the interpretation of the actual magnitude and impact of this risk should be viewed with some caution. Limitations frequently found in these observational studies comprise poor correction for possible confounders and scarce descriptions of the circumstances in which falls occurred [9,17-20]. This was illustrated by the review on NSAIDs and the risk of accidental falls presented in this thesis. The variability in methodology of the studies reviewed hindered the computation of a pooled fall risk for NSAIDs. Nevertheless, an increased risk for accidental falls in elderly using NSAIDs was deemed probable.

Thus far, most experimental studies on medication (other than benzodiazepines) failed to elucidate the actual fall risk. They usually focused on changes in psychomotor functioning after medication use and only few actually assessed fall-related motor or cognitive skills [21-23]. Therefore, studies presented in the second part of this thesis used challenging balance tasks, a time-critical obstacle avoidance task and a secondary cognitive task. With this extensive set of tests it was expected that CNS effects of medication suspected to lead to an increased fall risk could be revealed and clarified.

Firstly, we focused on NSAIDs since our systematic review showed that an increased risk for accidental falls is probable for elderly exposed to these drugs [24]. Indomethacin is part of the commonly used NSAID group and is known to cause CNS adverse effects [25]. We investigated the influence of this drug on fall-related skills in healthy seniors. Despite the fact that 40% of the participants of our study reported CNS adverse effects, no changes were found on either one of the fall-related tasks. It was concluded that indomethacin alone does not affect CNS functions such as mental alertness and motor coordination or other elements essential to the correct performance of the task. Thus it seems unlikely that indomethacin itself increases fall risk in seniors. It should be noted, however, that indomethacin is mostly used in the treatment of several inflammatory diseases.

More generally, since pain is a common symptom of such diseases, NSAIDs are often prescribed when paracetamol is insufficient to reduce this pain. Hence, pain could be an important (confounding) factor underlying fall risk after NSAID use. Previous research showed that pain is associated with an increased propensity to trip over an obstacle [26] and an increased fall risk in a general population of community-living older adults [27]. On the other hand, it is shown that pain-relief in knee osteoarthritis reduces the propensity to trip over an obstacle [28] and improves gait function [29]. Nevertheless, despite the pain-relief, the patients with knee osteoarthritis performed less than disease-free controls [28,29]. This indicates that pain itself is not a sufficient explanation for the deficiencies found in gait or obstacle avoidance. Factors other than CNS effects or pain, could possibly underlie the apparent increased fall risk with NSAID use found in several observational studies [30-33] and these factors remain to be investigated. Therefore it is suggested that future research should comprise prospective measurement of falls and extensive monitoring of medication use, pain and fall circumstances.

Selective serotonin reuptake-inhibitors (SSRIs) are another commonly prescribed medication group in the elderly and are used in the treatment of depression and anxiety. SSRIs also cause CNS adverse effects and are associated with an increased fall risk [18,34,35]. Therefore, a second study was performed using this type of medication. In this study, we assessed fall-related skills with the above mentioned extensive set of tests in seniors using an SSRI, paroxetine in particular. Only static balance control appeared to be affected in seniors using paroxetine compared to healthy age-matched controls. It seemed unlikely that this decrement was caused by anxiety or depression for a correlation between the scores on the HADS (Hospital Anxiety and Depression Scale [36]) and postural sway was lacking. A possible explanation for the increased fall risk found with SSRI use could be due to the effect of serotonin on the vestibular system, rather than on other fall-related CNS functions. However, this idea could not be supported since paroxetine did not seem to affect quiet standing on compliant surface with eyes closed. It was also hypothesized that paroxetine affected attentional capacities and hence, indirectly, balance capacities could be affected as well. Pacher and Ungvari [37] assumed cardiovascular effects such as orthostatic hypotension and arrhythmias to be another mechanism that could add to an increased fall risk with SSRI use. Hence, the relation between SSRI use and falls appears to be quite complex. Therefore, future research should focus on the reduction or even the elimination of possible confounding factors and prospectively monitor falls and their circumstances in seniors using SSRIs.

Complications in understanding the relation between medication use and fall risk

Even though we used tests proven to be sensitive enough to detect differences in a selection of CNS functions relevant to fall-related skills, differences due to CNS adverse effects of medication were only partly revealed in this thesis. However, it would be impetuous to conclude that these adverse effects have nothing to do with fall risk. Information on adverse effects of medication is usually based on reports of the users. Therefore, it is likely that these reports are subject to the degree a user experiences adverse effects. Hence, adverse effects mentioned in the leaflets appear to be rather subjective and do not necessarily reflect actual undesired (CNS) effects which may influence fall-related skills. It seems possible that other systems than the CNS play a role in the experience of such undesired effects as well. Whereas it is suggested that dizziness after SSRI use is likely to be caused by the effect of serotonin on the vestibular system [38,39], dizziness after use of other medication could also be vestibular of origin. Other commonly experienced CNS adverse effects are drowsiness or confusion. These effects could be due, for instance, to one's perception of his surroundings instead of changes in mental alertness due to medication use. Hence, it seems that experienced adverse effects often cannot be attributed to a single pathway. This is a complicating aspect in the understanding of the relation between medication use, its CNS effects on fall-related skills and a possibly increased fall risk. It becomes even more complex when drug-drug interactions result in CNS adverse effects.

Concluding remarks and recommendations

This thesis aimed to gain insight into the extent to which medication could affect fall-related skills in a senior population and, by doing so, to reduce possible accidental falls. We succeeded in composing a set of tests suitable and sensitive enough for the assessment of important CNS functions relevant to falls. We suggest that testing of fall-related skills is useful in assessing fall risk with medication use. Moreover, it is important to have various tests available for different medication classes affecting different CNS functions. The fact that we hardly found any significant effects of indomethacin and paroxetine could indicate that these drugs are relatively safe with regard to accidental falls. On the other

hand, we can also conclude that it remains difficult to quantitatively evaluate the effect of medication on mechanisms related to fall risk.

Concerning the reduction of possible medication-related accidental falls, a thorough evaluation of one's medication used and in addition the withdrawal of risk medication [40] has shown to be quite useful. Moreover, it is known that starting a new medication such as an anti-hypertensive agent, or anti-parkinsonian, anti-anxiety and hypnotic agents may act as a trigger for the onset of a fall [41]. The methods addressed in this thesis could be used to quantify the effect of either starting with medication or the withdrawal of risk medication on fall-related skills in the elderly. More specifically, it enables researchers or physicians to evaluate this effect on the level of the individual patient. However, performing the complete set of tasks might be too time- and energy-consuming for either the researcher or the patient, and requires laboratories in which the tests can be carried out. To make the reduction of medication-related falls successful, it is suggested that future research on this topic should address several aspects. Firstly, one should investigate which tests are most sensitive for the effects of a large variety of drugs. Next, one should aim to simplify those tests to make it possible to perform them with a little amount of time or resources. Finally, for a better understanding of the applicability of this approach, future experimental studies should aim to quantify the effect of both medication onset and withdrawal, preferably in large randomized controlled trials.

References

1. Weerdesteyn V, Nienhuis B, Duysens J: **Advancing age progressively affects obstacle avoidance skills in the elderly.** *Hum Mov Sci* 2005, **24:** 865-880.
2. Faulkner KA, Redfern MS, Cauley JA, Landsittel DP, Studenski SA, Rosano C *et al.*: **Multitasking: association between poorer performance and a history of recurrent falls.** *J Am Geriatr Soc* 2007, **55:** 570-576.
3. Chen HC, Ashton-Miller JA, Alexander NB, Schultz AB: **Effects of age and available response time on ability to step over an obstacle.** *J Gerontol* 1994, **49:** M227-M233.
4. Weerdesteyn V, Rijken H, Geurts AC, Smits-Engelsman BC, Mulder T, Duysens J: **A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly.** *Gerontology* 2006, **52:** 131-141.
5. Woollacott M, Shumway-Cook A: **Attention and the control of posture and gait: a review of an emerging area of research.** *Gait Posture* 2002, **16:** 1-14.
6. Yogev-Seligmann G, Hausdorff JM, Giladi N: **The role of executive function and attention in gait.** *Mov Disord* 2008, **23:** 329-342.
7. Shor RE: **An auditory analog of the Stroop Test.** *J Gen Psychol* 1975, **93:** 281-288.
8. Blake AJ, Morgan K, Bendall MJ, Dallosso H, Ebrahim SB, Arie TH *et al.*: **Falls by elderly people at home: prevalence and associated factors.** *Age Ageing* 1988, **17:** 365-372.
9. Daal JO, van Lieshout JJ: **Falls and medications in the elderly.** *Neth J Med* 2005, **63:** 91-96.
10. Lajoie Y, Gallagher SP: **Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers.** *Arch Gerontol Geriatr* 2004, **38:** 11-26.
11. Lord SR, Anstey KJ, Williams P, Ward JA: **Psychoactive medication use, sensori-motor function and falls in older women.** *Br J Clin Pharmacol* 1995, **39:** 227-234.
12. Lord SR, March LM, Cameron ID, Cumming RG, Schwarz J, Zochling J *et al.*: **Differing risk factors for falls in nursing home and intermediate-care residents who can and cannot stand unaided.** *J Am Geriatr Soc* 2003, **51:** 1645-1650.
13. Moylan KC, Binder EF: **Falls in older adults: risk assessment, management and prevention.** *Am J Med* 2007, **120:** 493-496.
14. Hawk C, Hyland JK, Rupert R, Colonvega M, Hall S: **Assessment of balance and risk for falls in a sample of community-dwelling adults aged 65 and older.** *Chiropr Osteopat* 2006, **14:** 3.
15. Schillings AM, Mulder T, Duysens J: **Stumbling over obstacles in older adults compared to young adults.** *J Neurophysiol* 2005, **94:** 1158-1168.
16. Thrane G, Joakimsen RM, Thornquist E: **The association between timed up and go test and history of falls: the Tromso study.** *BMC Geriatr* 2007, **7:** 1.
17. Cumming RG, Miller JP, Kelsey JL, Davis P, Arfken CL, Birge SJ *et al.*: **Medications and multiple falls in elderly people: the St Louis OASIS study.** *Age Ageing* 1991, **20:** 455-461.
18. Darowski A, Chambers SA, Chambers DJ: **Antidepressants and falls in the elderly.** *Drugs Aging* 2009, **26:** 381-394.
19. Leipzig RM, Cumming RG, Tinetti ME: **Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs.** *J Am Geriatr Soc* 1999, **47:** 30-39.
20. Leipzig RM, Cumming RG, Tinetti ME: **Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs.** *J Am Geriatr Soc* 1999, **47:** 40-50.
21. Bruce-Jones PN, Crome P, Kalra L: **Indomethacin and cognitive function in healthy elderly volunteers.** *Br J Clin Pharmacol* 1994, **38:** 45-51.
22. Draganich LF, Zacny J, Klafta J, Karrison T: **The effects of antidepressants on obstructed and unobstructed gait in healthy elderly people.** *J Gerontol A Biol Sci Med Sci* 2001, **56:** M36-M41.
23. Swift CG: **Postural instability as a measure of sedative drug response.** *Br J Clin Pharmacol* 1984, **18 Suppl 1:** 87S-90S.
24. Hegeman J, van den Bernt BJ, Duysens J, van Limbeek J: **NSAIDs and the risk of accidental falls in the elderly: a systematic review.** *Drug Saf* 2009, **32:** 489-498.
25. Seideman P, von Arbin M: **Cerebral blood flow and indomethacin drug levels in subjects with and without central nervous side effects.** *Br J Clin Pharmacol* 1991, **31:** 429-432.
26. Pandya NK, Draganich LF, Mauer A, Piotrowski GA, Pottenger L: **Osteoarthritis of the knees increases the propensity to trip on an obstacle.** *Clin Orthop Relat Res* 2005, 150-156.

27. Leveille SG, Jones RN, Kiely DK, Hausdorff JM, Shmerling RH, Guralnik JM *et al.*: **Chronic musculoskeletal pain and the occurrence of falls in an older population.** *JAMA* 2009, **302:** 2214-2221.
28. Pandya NK, Piotrowski GA, Pottenger L, Draganich LF: **Pain relief in knee osteoarthritis reduces the propensity to trip on an obstacle.** *Gait Posture* 2007, **25:** 106-111.
29. Shrader MW, Draganich LF, Pottenger LA, Piotrowski GA: **Effects of knee pain relief in osteoarthritis on gait and stair-stepping.** *Clin Orthop Relat Res* 2004, 188-193.
30. Kallin K, Gustafson Y, Sandman PO, Karlsson S: **Drugs and falls in older people in geriatric care settings.** *Aging Clin Exp Res* 2004, **16:** 270-276.
31. Kelly E, Darke S, Ross J: **A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions.** *Drug Alcohol Rev* 2004, **23:** 319-344.
32. Lee JS, Kwok T, Leung PC, Woo J: **Medical illnesses are more important than medications as risk factors of falls in older community dwellers? A cross-sectional study.** *Age Ageing* 2006, **35:** 246-251.
33. Ryynanen OP, Kivela SL, Honkanen R, Laippala P, Saano V: **Medications and chronic diseases as risk factors for falling injuries in the elderly.** *Scand J Soc Med* 1993, **21:** 264-271.
34. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N: **Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people.** *Lancet* 1998, **351:** 1303-1307.
35. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA: **Antidepressants and the risk of falls among nursing home residents.** *N Engl J Med* 1998, **339:** 875-882.
36. Zigmond AS, Snaith RP: **The hospital anxiety and depression scale.** *Acta Psychiatr Scand* 1983, **67:** 361-370.
37. Pacher P, Ungvari Z: **Selective serotonin-reuptake inhibitor antidepressants increase the risk of falls and hip fractures in elderly people by inhibiting cardiovascular ion channels.** *Med Hypotheses* 2001, **57:** 469-471.
38. Ramos RT: **Antidepressants and dizziness.** *J Psychopharmacol* 2006, **20:** 708-713.
39. Smith PF, Darlington CL: **A possible explanation for dizziness following SSRI discontinuation.** *Acta Otolaryngol* 2010, **130:** 981-983.
40. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ: **Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study.** *Br J Clin Pharmacol* 2007, **63:** 232-237.
41. Shuto H, Imakyure O, Matsumoto J, Egawa T, Jiang Y, Hirakawa M *et al.*: **Medication use as a risk factor for inpatient falls in an acute care hospital: a case-crossover study.** *Br J Clin Pharmacol* 2010, **69:** 535-542.

Summary

In Chapter 1 a general introduction is given on fall risk and medication as well as fall-related skills. It describes the association between medication and accidental falls in the elderly. Many epidemiological studies showed that medication use is an important risk factor for accidental falls; particularly drugs with commonly reported central nervous system (CNS) adverse effects. It is shown that withdrawal of such fall-risk-increasing drugs or even just lowering the dose significantly reduced fall risk in an elderly population. However, sensitive methods to quantitatively investigate the effect of this approach on fall risk and fall-related skills are still lacking. Therefore this thesis aimed to gain insight into the influence of commonly used medicines on fall-related skills. The studies described in this thesis investigated skills such as balance control, response to sudden events and dual tasking during gait.

As a commonly used social drug known to affect gait we used alcohol to investigate whether a time-critical obstacle avoidance is sensitive enough to detect changes in obstacle avoidance skills after intake of this chemical substance. Chapter 2 describes the study which served as a 'proof-of-principle'. Alcohol, even at low concentrations considered safe for driving, affects brain function and increases fall risk. An increased fall risk has been associated with impaired obstacle avoidance skills. Low level BACs (blood alcohol concentrations) are likely to affect obstacle avoidance reactions during gait, since the brain areas that are presumably involved in these reactions have been shown to be influenced by alcohol. Thirteen healthy senior individuals were subjected to an obstacle avoidance task on a treadmill after low alcohol consumption. Fast stepping adjustments were required to successfully avoid suddenly appearing obstacles. Response times and amplitudes of the m. biceps femoris (BF), a prime mover in avoidance reactions, as well as avoidance failure rates were assessed. After the first alcoholic drink, 12 of the 13 participants already had slower responses. Without exception, all participants' BF response times were delayed after the final alcoholic drink compared to when the participants were sober. The BF response times were significantly delayed from BACs of 0.035% onwards and were strongly associated with increasing levels of BAC. These delays had important behavioral consequences. Chances of hitting the obstacle were doubled with increased BACs. The results of this study clearly show that even with BACs considered to be safe for driving; obstacle avoidance reactions are inadequate, late, and too small.

Hence, we concluded that a time-critical obstacle avoidance task was sensitive enough to assess CNS (adverse) effects of medication.

To test whether dual-tasking could cause detectable subtle gait changes, Chapter 3 described the effect of a secondary cognitive task on gait under difficult circumstances. Bilaterally asymmetric stepping during walking common to a number of pathological gaits (e.g. hemiplegia, limping). In the present study, the attention level of asymmetric stepping was studied by having young adults walk on a split-belt treadmill with symmetric (2 km/h) and asymmetric (2 km/h vs 4 km/h and 2 km/h vs 6 km/h) belt speeds both with and without a secondary auditory Stroop task. There was no significant change in verbal response time reactions across walking conditions or between walking and standing. The proportion of stance phase was unchanged by the secondary task during symmetric walking. Stance phase proportions, however, significantly increased during dual tasking for the limb on the faster belt for asymmetric conditions, while they decreased for the limb on the slower belt for the most asymmetric condition. There were also small modifications to double support proportions and a main effect of dual tasking to double support variability. Observed dual task changes showed interference by the cognitive task with asymmetric gait performance, suggesting that asymmetric stepping, such as seen in limping gaits, requires more attention than symmetric walking. Such attention may, in part, be due to the dynamic balance required in asymmetric limb loading and unloading. Hence, this study demonstrated that the auditory Stroop task was useful to detect small changes in gait when it becomes less automatic.

Dual-tasking can lead to falls, as does a deterioration of obstacle avoidance skills. Hence, it is expected that a combination of both would be even more detrimental, especially when obstacles have to be avoided under time pressure. Previous work confirmed this expectation; however, due to several limitations in the design of previous studies it is yet too early to draw any definitive conclusions on the allocation of attentional resources in obstacle avoidance under dual-task conditions. Therefore, the study presented in Chapter 4 used a primary and secondary task that were both attentionally demanding, with the instruction to perform as well as possible on both tasks, and evaluated this with highly sensitive outcome parameters. Nineteen healthy senior individuals performed an obstacle avoidance task on a treadmill while walking at 3km/h as a single task and combined with an auditory Stroop task. M. biceps femoris (BF) response times and obstacle avoidance failure

rates were assessed. For the secondary task a composite score ((100xaccuracy)/ verbal response time) was computed. Increased obstacle avoidance failure rates (3%) and delayed BF response times (21ms) were found under dual-task conditions. Composite scores were reduced during and just after obstacle crossing. We concluded that dual-tasking while avoiding obstacles under time pressure affects the motor as well as the cognitive task when subjects are instructed to keep up their performance on both. These findings add to the evidence indicating an increased risk of tripping or falling when attention is divided during walking over uneven terrain. In addition, it is suggested that the dual-task paradigm of a time-critical obstacle avoidance task combined with an auditory secondary task can be a useful method to investigate CNS adverse effects of medication.

In the second part of this thesis we used the tasks to assess fall-related skills to gain insight into the fall risk after use of drugs frequently prescribed as a treatment for two important chronic conditions in the elderly: rheumatic and psychosocial diseases. In Chapter 5 a systematic literature review is given on NSAIDs (non-steroidal anti-inflammatory drugs) and the risk of accidental falls in the elderly. Accidental falls, especially those occurring in the elderly, are a major health and research topic nowadays. Besides environmental hazards and the physiological changes associated with ageing, medication use (e.g. benzodiazepines, vasodilators and antidepressants) and polypharmacy are significant risk factors for falling as well. Exposure to NSAIDs has been associated with accidental falls too, although information on this area is less consistent. Therefore, the main goal of this review was to provide an updated overview of all the evidence published on risk of falling due to NSAID use so far. Validity and data extraction of eligible articles was assessed by adapted criteria, based on checklists that were originally developed to assess case-control or cohort studies. From the 16 selected articles, two studies were rejected due to clustering of data and one article was excluded because it contained the same data as that in one of the included articles. None of the articles included a randomized controlled trial. The remaining 13 studies all showed some lack in completeness of their statistical methods, and much variation in reporting of effects. The overall mean age was high in the study populations, leaving the results to be poorly generalizable to a larger population and other age categories. Despite these imperfections, all studies showed an increased risk of falling due to NSAID use (four significant, nine non-significant), and a tendency towards an increased fall risk with NSAID exposure could be noted. It is suggested that an increased risk for accidental falls is probable when elderly individuals are exposed to NSAIDs.

Increased reaction time and impaired postural balance have been determined as reliable predictors for those at risk of falling and are important functions of the central nervous system (CNS). An essential risk factor for falls is medication exposure. As shown in the previous chapter, NSAIDs are amongst the medications related to accidental falls. About 1-10% of all users experience CNS side effects. These side effects, such as dizziness, headaches, drowsiness, mood alteration, and confusion, seem to be more common during treatment with indomethacin. Hence, it is possible that maintenance of (static) postural balance and swift reactions to stimuli are affected by exposure to NSAIDs, indomethacin in particular, consequently putting older individuals at a greater risk for accidental falls. Therefore, the study presented in Chapter 6 investigated the effect of a high indomethacin dose in healthy middle-aged individuals on important predictors of falls: postural balance and reaction time. Twenty-two healthy middle-aged individuals participated in this double-blind, placebo-controlled, randomized crossover trial. Three measurements were conducted with a week interval each. A measurement consisted of postural balance as a single task and while concurrently performing a secondary cognitive task and manual reaction time tasks. For the first measurement indomethacin 75mg (slow-release) or a visually identical placebo was randomly assigned. In total, 5 capsules were taken orally in the 2.5 days preceding assessment. The second measurement was without intervention, for the final one the first placebo group got indomethacin and vice versa. Repeated measures GLM revealed no significant differences between indomethacin, placebo, and baseline in any of the balance tasks. No differences in postural balance were found between the single and dual task conditions, or on the performance of the dual task itself. Similarly, no differences were found on the manual reaction time tasks. The present study showed that a high indomethacin dose does not negatively affect postural balance and manual reaction time in this healthy middle-aged population. Although the relatively small and young sample limits the direct ability to generalize the results to a population at risk of falling, the results indicate that indomethacin alone is not likely to increase fall risk, as far as this risk is related to the abovementioned important functions of the CNS, and not affected by comorbidities.

CNS side effects are more common during treatment with indomethacin compared to other NSAIDs. In many European countries as well as in the USA, the leaflet or even the packaging of indomethacin contains a specific warning to refrain from activities requiring mental alertness and motor coordination, such as driving a

car. In Chapter 7 a placebo-controlled randomized study with cross-over design is presented which aimed to find evidence for the above mentioned warning. Indomethacin 75mg slow-release or a visually identical placebo with similar flavor was taken in orally twice daily for 2.5 days. It was suggested that indomethacin affects the motor coordination required to successfully avoid obstacles during walking and that this effect will be even stronger when simultaneously performing a cognitive task puts mental alertness to the test. Nineteen healthy middle-aged individuals were subjected to a time-critical obstacle avoidance task combined with a cognitive secondary task. Fast stepping adjustments were required to successfully avoid the obstacle, which was suddenly dropped on the treadmill. Both BF response times and avoidance failure rates were assessed. No differences between indomethacin and placebo were found on the outcome measures regarding motor coordination, avoidance failure rates and BF response times, nor on the performance on the secondary cognitive task. This study showed that tasks which demand maximum attention remain unaffected by a high dose of indomethacin despite the frequently reported CNS side effects such as dizziness, drowsiness and headaches. A high dose of indomethacin did not affect capabilities deemed essential for safe walking in healthy senior individuals. Hence, it is suggested that there might be no need to caution patients who experience CNS side effects after indomethacin use to avoid activities requiring quick and adequate reactions, such walking under challenging circumstances and maybe also driving a car.

SSRIs (selective serotonin reuptake inhibitors) are widely used to treat depression and are also associated with an increased falls risk. However, the biological mechanism underlying accidental falls with SSRI intake has yet to be elucidated. Hence, there is a need for specific tests and behavioral studies to assess this mechanism. The study presented in Chapter 8 was designed to investigate whether obstacle avoidance skills in long-term (>90 days), senior paroxetine users are affected during gait, simple and challenging postural balance tasks, as well as during manual reaction time tasks. The performance of the paroxetine users was compared with healthy group-matched controls. The results demonstrated impaired postural balance in the paroxetine users, especially during one-legged stance or under various dual-task conditions. Although the deficit in one-legged stance could indicate vestibular involvement, this was deemed unlikely since performance of standing on compliant surface with closed eyes remained unaffected. Paroxetine use also failed to affect manual reaction

times or obstacle avoidance performance. It is suggested that paroxetine affects attentional capacities particularly in conjunction with balance control. Compared to healthy seniors, senior long-term paroxetine users appear to be at an increased risk of falling due to impairments in balance control, especially when attention has to be divided between two concurrent activities.

Finally, in Chapter 9 an outline of the main findings and conclusions of this thesis were presented. The limitations of the presented studies were discussed and recommendations for future research were given.

Samenvatting

In hoofdstuk 1 wordt een algemene inleiding gegeven op zowel valrisico en medicatie als op valgerelateerde vaardigheden. Er wordt een beschrijving gegeven van de relatie tussen medicatie en valpartijen bij ouderen. Verschillende epidemiologische studies hebben aangetoond dat medicijngebruik een belangrijke risicofactor voor valpartijen is, in het bijzonder medicijnen waarbij vaak bijwerkingen gerelateerd aan het centrale zenuwstelsel (CZS) gemeld worden. Eerder onderzoek heeft aangetoond dat het stoppen met een dergelijk valrisico verhogend medicijn of zelfs slechts het verlagen van de dosis een aanzienlijke vermindering van het valrisico bij ouderen tot gevolg heeft. Het ontbreekt echter nog aan gevoelige methoden om het effect van deze aanpak op valrisico en valgerelateerde vaardigheden kwantitatief te kunnen onderzoeken. Zodoende heeft dit proefschrift als doel inzicht te krijgen in de invloed van veelgebruikte medicijnen op valgerelateerde vaardigheden. In de studies die beschreven worden in dit proefschrift werden vaardigheden zoals balans controle, reacties op plotselinge gebeurtenissen en het uitvoeren van dubbeltaken tijdens lopen onderzocht.

Hoofdstuk 2 beschrijft de studie die diende als een 'proof-of-principle'. Het is algemeen bekend dat alcohol consumptie het lopen negatief kan beïnvloeden. Vandaar dat we alcohol gebruikt hebben om te onderzoeken of een tijd-kritische obstakelontwijktaak gevoelig genoeg is om veranderingen waar te nemen in het vermogen om obstakels te ontwijken na inname van alcohol. Het is gebleken dat promillages waarbij autorijden wettelijk nog is toegestaan al van invloed zijn op hersenfuncties en het valrisico verhogen. Een verhoogd valrisico in het algemeen wordt geassocieerd met een verminderd vermogen obstakels te kunnen ontwijken tijdens lopen. De verwachting was dat zelfs lage promillages obstakel ontwijkreacties zouden beïnvloeden, omdat is aangetoond dat de hersengebieden die vermoedelijk betrokken zijn bij deze reacties worden beïnvloed door alcohol. Dertien gezonde oudere personen voerden een obstakelontwijktaak uit op een loopband na lage tot matige alcoholconsumptie. Om de plotseling verschijnende obstakels succesvol te ontwijken waren snelle stapreacties noodzakelijk. Naast successcores werden ook reactietijden en amplitudes van de m. biceps femoris (BF), een spier die vroeg geactiveerd wordt in ontwijkreacties, gemeten. Na de eerste alcoholische drank waren de ontwijkreacties van 12 van de 13 deelnemers al vertraagd. Zonder uitzondering waren de ontwijkreacties van alle deelnemers

vertraagd na de laatste alcoholische drank in vergelijking tot de conditie waarbij iedereen nuchter was. Vanaf een promillage van 0.35‰ waren de gemiddelde BF reactietijden significant langzamer en werd er een sterk verband gevonden tussen deze reactietijden en een toename in BAC. De langzame reacties hadden tot gevolg dat de kans om het obstakel te raken was verdubbeld bij hogere promillages. De resultaten van deze studie laten duidelijk zien dat obstakelontwijkreacties na de inname van alcohol onvoldoende en te laat zijn, zelfs bij promillages die nog als veilig worden beschouwd voor autorijden. Op basis van deze resultaten hebben we geconcludeerd dat een tijd-kritische obstakelontwijktaak gevoelig genoeg is om de (negatieve) effecten van medicatie op het centrale zenuwstelsel te kunnen meten.

Om te testen of het uitvoeren van een dubbeltaak tot waarneembare subtiele veranderingen in de manier van lopen zou leiden, beschrijft hoofdstuk 3 het effect van een secundaire cognitieve taak op lopen onder moeilijke omstandigheden. Een asymmetrisch looppatroon wordt bijvoorbeeld gezien bij mensen met hemiplegie of manklopen als gevolg van een andere aandoening. In deze studie werd onderzocht hoe het gesteld was met het aandachtsniveau tijdens asymmetrisch lopen. Jong volwassenen liepen hiervoor op een dubbele loopband (ieder been op 1 band) met symmetrische (2 km/u) en asymmetrische (2 km/u vs 4 km/u en 2 km/u vs 6 km/u) bandsnelheden zowel met als zonder een secundaire cognitieve taak. Er was geen significante verandering in verbale reactietijden tussen de verschillende loopcondities of tussen lopen en staan. Tijdens symmetrisch lopen bleef het aandeel van de standfase onveranderd door de secundaire taak. De verhouding standfase:zwaaifase nam echter aanzienlijk toe tijdens het uitvoeren van een cognitieve taak in combinatie met asymmetrisch lopen voor het been op de snelle band, terwijl deze verhouding afnam voor het been op de langzamere band bij de meest asymmetrische conditie. Tevens werden er kleine veranderingen gevonden in de periodes dat beide voeten tegelijk contact maakten met de ondergrond. Hierbij speelde het uitvoeren van de secundaire cognitieve taak een hoofdrol. Deze veranderingen toonden aan dat asymmetrisch lopen beïnvloed werd door de secundaire taak, wat suggereert dat zo'n looppatroon meer aandacht vereist dan symmetrisch lopen. Dit kan voor een deel te wijten zijn aan de dynamische balans die nodig is bij de asymmetrische belasting van de ledematen. Dit onderzoek heeft aangetoond dat het gebruik van een secundaire cognitieve taak nuttig was om subtiele veranderingen in het looppatroon teweeg te brengen wanneer het lopen minder automatisch gaat, zoals bijvoorbeeld bij manklopen.

Zowel het uitvoeren van dubbeltaken als een verminderd vermogen om obstakels te ontwijken tijdens lopen kunnen leiden tot valpartijen. Een combinatie van beide zou mogelijk nog desastreuzer zijn, vooral als obstakels moeten worden vermeden onder tijdsdruk. Eerdere onderzoeken bevestigden dit vermoeden, maar door een aantal beperkingen in het ontwerp van deze onderzoeken is het nog te vroeg om definitieve conclusies te trekken over de verdeling van aandacht wanneer obstakels ontweken moeten worden onder dubbeltaak omstandigheden. Daarom is in het onderzoek dat gepresenteerd wordt in hoofdstuk 4 gebruik gemaakt van een primaire en secundaire taak die beiden veel concentratie vereisen. De proefpersonen kregen hierbij de opdracht zo goed mogelijk te presteren op beide taken en dit werd geëvalueerd met gevoelige uitkomstparameters. Negentien gezonde oudere personen voerden een obstakelontwijktaak uit op een loopband (3km/u) als een enkele taak en gecombineerd met een secundaire cognitieve taak. Naast successcores werden ook reactietijden en amplitudes van de m. biceps femoris (BF), een spier die vroeg geactiveerd wordt in ontwijkreacties, gemeten. Voor de secundaire taak werd een composiet score ((100xnauwkeurigheid) / verbale reactietijd) berekend. Onder dubbeltaak omstandigheden werden er meer obstakels geraakt (3%) en daarbij waren de obstakel ontwijkreacties vertraagd (21ms). De composiet scores waren aanzienlijk lager tijdens en vlak na het ontwijken van het obstakel in vergelijking tot daarvoor. Hieruit concludeerden we dat onder dubbeltaak condities zowel het vermijden van obstakels onder tijdsdruk als de cognitieve taak negatief worden beïnvloed wanneer hierbij de instructie gegeven is om op beide taken zo goed mogelijk te presteren. Deze bevindingen dragen bij aan de aanwijzingen uit eerder onderzoek dat er een verhoogd risico op struikelen of vallen ontstaat wanneer de aandacht verdeeld moet worden tijdens het lopen op oneffen of onbekend terrein. Daarnaast lijkt het dubbeltaak-paradigma van een tijd-kritische obstakelontwijktaak in combinatie met een auditieve secundaire taak tevens een bruikbare methode om CZS-gerelateerde bijwerkingen van medicatie te onderzoeken omdat op deze manier subtiele veranderingen te detecteren zijn.

In het tweede deel van dit proefschrift hebben we de taken die valgerelateerde vaardigheden testen gebruikt om inzicht te krijgen in het valrisico na gebruik van medicijnen die vaak worden voorgeschreven in de behandeling van twee chronische aandoeningen bij ouderen: reumatische en psychosociale aandoeningen. Hoofdstuk 5 presenteert een systematisch literatuuronderzoek naar NSAIDs (niet-steroïdale anti-inflammatoire drugs) en het risico op valpartijen bij

ouderen. Tegenwoordig zijn valpartijen bij ouderen een belangrijk gezondheids- en onderzoeksonderwerp. Naast omgevingsgerelateerde risicofactoren en de fysiologische veranderingen die gepaard gaan met het ouder worden, zijn het gebruik van geneesmiddelen zoals benzodiazepines, vasodilatoren en antidepressiva, en polyfarmacie eveneens belangrijke risicofactoren voor vallen. Gebruik van NSAIDs is ook geassocieerd met valpartijen, alleen is de informatie op dit gebied minder consistent. Daarom was het belangrijkste doel van dit literatuuronderzoek om een actueel overzicht te krijgen van alle onderzoeken die tot nu toe gepubliceerd hebben over het risico van vallen als gevolg van NSAID-gebruik. Op basis van checklists die oorspronkelijk zijn ontwikkeld om de kwaliteit van case-control- of cohort studies te beoordelen zijn aangepaste criteria opgesteld om de validiteit en data-extractie van de geselecteerde artikelen te beoordelen. Van de 16 geselecteerde artikelen, zijn twee studies uitgesloten als gevolg van clustering van gegevens en een derde artikel is uitgesloten omdat daarin dezelfde gegevens gebruikt waren als in één van de geschikte artikelen. Tussen de geschikte artikelen zat geen gerandomiseerde gecontroleerde trial. De overige 13 artikelen gaven veelal een onvolledige beschrijving van de statistische methoden en ook werd veel variatie in de beschrijving van de effecten gevonden. De gemiddelde leeftijd was doorgaans hoog in de bestudeerde groepen waardoor generalisatie naar grotere groepen en andere leeftijdscategorieën bemoeilijkt werd. Ondanks deze onvolkomenheden vertoonden alle studies een verhoogd risico op vallen als gevolg van gebruik van NSAIDs (vier significant, negen niet-significant) en een tendens naar een verhoogd valrisico met NSAID-gebruik werd zichtbaar. Het lijkt daarom goed mogelijk dat er sprake is van een verhoogd valrisico bij ouderen die NSAIDs gebruiken.

Een adequaat reactievermogen en balanscontrole zijn belangrijke functies van het centrale zenuwstelsel (CZS) en een verslechtering van deze functies is een belangrijke voorspeller voor valpartijen gebleken. Een andere belangrijke risicofactor voor vallen is het gebruik van medicatie. Zoals beschreven in het vorige hoofdstuk behoren NSAIDs tot de medicijnen mogelijk een verband hebben met valpartijen. Ongeveer 1-10% van alle gebruikers ervaren bijwerkingen die gerelateerd zijn aan het CZS. Deze bijwerkingen, zoals duizeligheid, hoofdpijn, sufheid, stemmingsverandering en verwarring lijken vaker voor te komen bij gebruik van indometacine. Het lijkt waarschijnlijk dat de balanscontrole en snelle reacties op stimuli worden beïnvloed door gebruik van NSAIDs, indometacine in het bijzonder, waardoor oudere gebruikers een groter risico lopen om te vallen.

Het onderzoek dat in hoofdstuk 6 gepresenteerd wordt onderzocht daarom bij gezonde oudere personen wat het effect was van een hoge dosis indometacine op belangrijke voorspellers van vallen: het evenwicht en reactietijd. Tweeëntwintig gezonde personen van middelbare leeftijd namen deel aan deze dubbelblinde, placebo-gecontroleerde, gerandomiseerde cross-over trial. Er werden drie metingen uitgevoerd met daartussen steeds een week interval. Iedere meting bestond uit handreactietijdtaken en verschillende balansstaken waarbij sommigen ook herhaald werden terwijl gelijktijdig een secundaire cognitieve taak uitgevoerd werd. Indometacine 75 mg (slow-release) of een visueel identiek placebo werd willekeurig toegewezen voor de eerste meting. Iedere proefpersoon slikte in totaal vijf capsules in de 2,5 dagen voorafgaand aan de meting. De tweede meting was zonder inname van capsules (baseline) en voor de laatste meting kregen de proefpersonen die in eerste instantie indometacine slikten nu placebo en andersom. Statistische toetsing toonde aan dat er geen significante verschillen waren in de prestaties op de balansstaken tussen indomethacine, placebo en baseline. Ook werden er geen verschillen in de balansstaken gevonden met en zonder de gelijktijdige uitvoering van een secundaire cognitieve taak, of op de prestaties van deze secundaire taak zelf. Daarnaast zijn er eveneens geen verschillen gevonden in de prestaties op de handreactietijdtaken. De huidige studie toonde aan dat een hoge dosis indometacine geen negatieve gevolgen heeft voor de balanshandhaving of handreactietijd bij gezonde mensen van middelbare leeftijd. Generalisatie van deze resultaten naar oudere mensen met een verhoogd valrisico is beperkt doordat we een relatief kleine en jonge groep proefpersonen onderzocht hebben. Echter deze resultaten geven ook aan dat gebruik van indometacine alléén het valrisico waarschijnlijk niet verhoogd, voor zover dit risico is gerelateerd aan de bovengenoemde belangrijke functies van het CZS en niet beïnvloed is door andere aandoeningen.

Bijwerkingen van het CZS komen vaker voor tijdens gebruik van indometacine in vergelijking tot andere NSAIDs. In veel Europese landen, maar ook in de Verenigde Staten staat er in de bijsluiter of zelfs op de verpakking van indometacine een specifieke waarschuwing om activiteiten te vermijden waarbij concentratie en coördinatie nodig is, zoals als het besturen van een auto. In hoofdstuk 7 wordt een placebo-gecontroleerde gerandomiseerde studie met cross-over design gepresenteerd die gericht was op het vinden van een bewijs voor de bovengenoemde waarschuwing. Iedere proefpersoon slikte in totaal vijf capsules indometacine 75 mg slow-release of een visueel identiek placebo met vergelijkbare

smaak in de 2,5 dagen voorafgaand aan de meting. Er werd gesuggereerd dat indometacine de coördinatie die nodig is om tijdens lopen succesvol obstakels te kunnen ontwijken negatief zou beïnvloeden en dat dit effect sterker zou worden wanneer gelijktijdig een cognitieve taak uitgevoerd werd waarbij mentale alertheid op de proef werd gesteld. Negentien gezonde oudere personen voerden een obstakelontwijktaak uit op een loopband (3km/u) als een enkele taak en gecombineerd met een secundaire cognitieve taak. Om de plotseling verschijnende obstakels succesvol te ontwijken waren snelle stapreacties noodzakelijk. Naast successcores werden ook reactietijden en amplitudes van de m. biceps femoris (BF), een spier die vroeg geactiveerd wordt in ontwijkreacties, gemeten. Voor de secundaire taak werd een composiet score ((100xnauwkeurigheid) / verbale reactietijd) berekend. Statistische toetsing liet zien dat er geen verschillen waren tussen indometacine en placebo op de uitkomstparameters die betrekking hadden op de coördinatie: successcores en BF reactietijden, noch verschilden de prestaties op de secundaire cognitieve taak. Deze studie toonde aan dat taken die maximale aandacht vragen niet beïnvloed lijken te worden door een hoge dosis indometacine, ondanks de vaak gemelde CZS bijwerkingen zoals duizeligheid, slaperigheid en hoofdpijn. Een hoge dosis indometacine lijkt geen invloed te hebben op vaardigheden die essentieel worden geacht voor gezonde ouderen om veilig te kunnen lopen. Daarom suggereren we dat patiënten die CZS bijwerkingen ondervinden na gebruik van indometacine misschien niet gewaarschuwd hoeven te worden om activiteiten te vermijden die snelle en adequate reacties vereisen, zoals het lopen onder moeilijke omstandigheden en misschien zelfs het besturen van een auto.

SSRIs (selectieve serotonine heropname remmers) worden veel gebruikt om depressie te behandelen en zijn daarnaast ook geassocieerd met een verhoogd valrisico. Echter, het biologische mechanisme achter valpartijen bij SSRI gebruik is nog onduidelijk. Hierdoor is er een behoefte aan specifieke tests en experimentele studies om dit mechanisme te verhelderen. De studie die gepresenteerd wordt in hoofdstuk 8 was ontworpen om te onderzoeken of langduring gebruik van paroxetine (> 90 dagen) door ouderen van invloed is op het vermogen om obstakels vermijden tijdens lopen, balanscontrole en handreactietijd. De prestaties van de paroxetine-gebruikers werd vergeleken met gezonde controlepersonen van dezelfde leeftijd en geslacht. De resultaten toonden aan dat de balanscontrole verminderd was bij de paroxetine-gebruikers, met name tijdens staan op één been of onder verschillende dubbeltaak

omstandigheden. Hoewel deze verminderde balanscontrole een vestibulaire oorzaak zou kunnen hebben, werd dit beschouwd als onwaarschijnlijk omdat de balanscontrole tijdens staan op zachte ondergrond met gesloten ogen niet verminderd was. Paroxetine bleek de handreactietijden of het vermogen obstakels te ontwijken niet te beïnvloeden. Er wordt daarom gesuggereerd dat paroxetine met name van invloed is op het concentratievermogen in combinatie met balanscontrole. In vergelijking met gezonde ouderen lijken de paroxetine gebruikers een verhoogd risico op vallen te hebben als gevolg van verminderde balanscontrole, vooral wanneer de aandacht moet worden verdeeld tussen twee gelijktijdige activiteiten.

Tenslotte wordt in hoofdstuk 9 een overzicht gegeven van de belangrijkste bevindingen en conclusies van dit proefschrift. Daarnaast worden de beperkingen van de gepresenteerde studies besproken en aanbevelingen voor toekomstig onderzoek gegeven.

List of publications

Articles in international journals

Hegeman J, Honegger F, Kupper M, Allum JH: **The balance control of bilateral peripheral vestibular loss subjects and its improvement with auditory prosthetic feedback.** *J Vestib Res* 2005, **15:** 109-117.

Hurk van den HP, Mars RB, van EG, Hegeman J, Pasman JW, Bloem BR *et al.*: **Online maintenance of sensory and motor representations: effects on corticospinal excitability.** *J Neurophysiol* 2007, **97:** 1642-1648.

Hegeman J, Shapkova EY, Honegger F, Allum JH: **Effect of age and height on trunk sway during stance and gait.** *J Vestib Res* 2007, **17:** 75-87.

Oude Nijhuis LB, Hegeman J, Bakker M, Van Meel M, Bloem BR, Allum JH: **The influence of knee rigidity on balance corrections: a comparison with responses of cerebellar ataxia patients.** *Exp Brain Res* 2008, **187:** 181-191.

Hegeman J, van den Bemt BJ, Duysens J, van Limbeek J: **NSAIDs and the risk of accidental falls in the elderly: a systematic review.** *Drug Saf* 2009, **32:** 489-498.

McFadyen BJ, Hegeman J, Duysens J: **Dual task effects for asymmetric stepping on a split-belt treadmill.** *Gait Posture* 2009, **30:** 340-344.

Hegeman J, Weerdesteyn V, van den Bemt BJ, Nienhuis B, van Limbeek J, Duysens J: **Even low alcohol concentrations affect obstacle avoidance reactions in healthy senior individuals.** *BMC Res Notes* 2010, **3:** 243.

Hegeman J, Nienhuis B, van den Bemt B, Weerdesteyn V, van Limbeek J, Duysens J: **The effect of a non-steroidal anti-inflammatory drug on two important predictors for accidental falls: Postural balance and manual reaction time. A randomized, controlled pilot study.** *Hum Mov Sci* 2011, **30:** 384-395.

Hegeman J, Weerdesteyn V, van den Bemt BJ, Nienhuis B, van Limbeek J, Duysens J: **Dual-tasking interferes with obstacle avoidance reactions in healthy seniors.** *Submitted*

Hegeman J, van den Bemt BJ, Weerdesteyn V, Nienhuis B, van Limbeek J, Duysens J: **CNS-effects of indomethacin, should patients really be cautioned about decreased mental alertness and motor coordination?** *Submitted*

Hegeman J, van den Bemt BJ, Weerdesteyn V, Nienhuis B, van Limbeek J, Duysens J: **Unravelling the association between SSRI use and falls: An experimental study of risk factors for accidental falls in long-term paroxetine users.** Accepted with minor revisions by *Clin Neuropharmacol*

Conference abstracts

John HJ Allum, Lars Oude Nijhuis, Judith Hegeman, Flurin Honegger. **Quadrophonic auditory feedback of trunk sway for improving balance control during stance and gait tasks.** *ARO Midwinter Meeting, February 2004, Florida, USA*

John HJ Allum, Judith Hegeman, Lars Oude Nijhuis, Flurin Honegger. **Auditory feedback prosthesis for improving balance control during stance and gait tasks.** *Bárány Society, XXIII Int. Congress, July 2004, Paris, France*

M. van Meel, J. Hegeman, J.H.J. Allum, M. Majewsky and B.R. Bloem. **The influence of artificially induced knee "locking" on balance corrects**. *XVIIth Conference on Postural and Gait Research, June 2005, Marseille, France*

J.H.J. Allum, J. Hegeman, L.B. Oude Nijhuis and F. Honegger. **Auditory feedback prosthesis for improving balancecontrol during stance and gait tasks.** *XVIIth Conference on Postural and Gait Research, June 2005, Marseille, France*

BJF van den Bemt, J Hegeman, R Janknegt, FH van den Hoogen, HB Benraad, J van Limbeek. **Variability in dosing and costs of the TNFa-antagonists adalimumab and etanercept in patients with inflammatory rheumatic diseases.** *European League against Rheumatism, June 2006, Amsterdam, The Netherlands*

BJF van den Bemt, J Hegeman, FH van den Hoogen, HB Benraad. **Quality differences between commercially available glucosamine products.** *European League against Rheumatism, June 2006, Amsterdam, The Netherlands*

J Hegeman, B van den Bemt, V Weerdesteyn, B Nienhuis, J van Limbeek, J Duysens. **Effects of dual tasking on obstacle avoidance ability and onset latency in healthy subjects using indomethacin.** *Gait & Mental Function, February 2008, Amsterdam, The Netherlands*

BJ McFadyen, J Hegeman, J Duysens. **The effects of simultaneously responding to an auditory task during split-belt treadmill walking with symmetric and asymmetric timing.** *Gait & Mental Function, February 2008, Amsterdam, The Netherlands*

Judith Hegeman, Bart Nienhuis, Bart van den Bemt, Vivian Weerdesteyn, Jacques van Limbeek, Jacques Duysens. **Indomethacin does not influence postural control in healthy middle-aged individuals.** *ISPGR XIX Satellite PreConference, June 2009, Pavia, Italy*

Judith Hegeman, Bart Nienhuis, Bart van den Bemt, Vivian Weerdesteyn, Jacques van Limbeek, Jacques Duysens. **Indomethacin does not influence postural control and manual reaction time in healthy middle-aged individuals.** *XIXth Conference on Postural and Gait Research, June 2009, Bologna, Italy*

Judith Hegeman, Vivian Weerdesteyn, Bart van den Bemt, Bart Nienhuis, Jacques van Limbeek, Jacques Duysens. **Avoid alcohol, avoid falling?** *XIXth Conference on Postural and Gait Research, June 2009, Bologna, Italy*

Judith Hegeman, Vivian Weerdesteyn, Bart van den Bemt, Bart Nienhuis, Jacques van Limbeek, Jacques Duysens. **Low level alcohol consumption compromises safe obstacle avoidance during gait.** *Neuroscience 2009, the 39th annual meeting of the Society for Neuroscience (SfN), October 2009, Chicago, USA*

Dankwoord

Curriculum Vitae

Dankwoord

Het was een mooie zomerdag in juni 2004. Bas Bloem hield een praatje bij mijn afstuderen en zei: "Onderzoek begint met een goed idee en de rest is bloed, zweet en tranen… *Ik* had een goed idee…". Twee jaar later kwamen Bart van den Bemt en Jaak Duysens met een goed idee. Tja, nu mijn proefschrift klaar is ben ik 'de rest' eigenlijk al bijna vergeten. Wat ik niet vergeten zal zijn alle collega's, familie en (sport-)vrienden die direct of indirect hebben bijgedragen aan de totstandkoming van mijn proefschrift, waarvan ik een aantal mensen in het bijzonder wil bedanken.

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Want er is altijd een boot naar de horizon
En een vliegtuig naar de plek daar waar de wereld ooit begon
Of een luchtballon, avonturen tegemoet
En een boekje waarin staat hoe het moet
Dus wees niet bang dat je dood gaat
Of dat de wereld bijt
Bedank maar dat als je hier blijft dat uiteindelijk de tijd zich blijft herhalen
Dus ga je mee verdwalen?

(Ernst van der Pasch, Verdwalen)

Curriculum Vitae

Judith Hegeman werd geboren op 16 juli 1977 te Huissen. Ze behaalde haar VWO diploma aan het Lorentz College te Arnhem in 1995. Na een jaar Vrijetijdskunde gestudeerd te hebben begon Judith in 1996 aan de opleiding tot Fysiotherapeut aan de Hogeschool Arnhem Nijmegen. In december 2000 behaalde ze haar diploma, waarna ze als waarnemend fysiotherapeut aan het werk ging in een verpleeghuis, revalidatiecentrum en particuliere praktijk. Vervolgens begon ze acht maanden later aan Radboud Universiteit Nijmegen aan de verkorte opleiding Biomedische Wetenschappen met als hoofdvak Bewegingswetenschappen. Tijdens deze opleiding deed ze een grote stage bij de afdeling Neurologie van het UMCN St. Radboud. Vanaf oktober 2003 combineerde ze een korte stage met haar eerste wetenschappelijke baan in het lab van professor JHJ Allum in Basel, Zwitserland. Na haar afstuderen in 2004 werkte Judith nog een aantal maanden in Zwitserland. Vervolgens had ze verschillende banen in Nederland en in september 2005 begon Judith als onderzoeksmedewerker bij de afdeling Farmacie van de Sint Maartenskliniek in Nijmegen. Een jaar later stapte ze over naar de afdeling Research, Development & Education waar startte ze met haar promotie-onderzoek naar valrisico bij geneesmiddelen. Dit proefschrift beschrijft de resultaten van dat onderzoek. Naast haar promotie-onderzoek werkte Judith sinds 2008 mee aan de oprichting van de CRO Sint Maartenskliniek Nijmegen. Vanaf juni 2011 is Judith werkzaam als trialcoördinator en projectmanager bij het Wetenschapsbureau van Ziekenhuis Rijnstate in Arnhem. Hier biedt ze onder andere ondersteuning bij de opzet, toetsing en uitvoering van wetenschappelijk onderzoek in het ziekenhuis.

Judith Hegeman was born on July 16, 1977 in Huissen. After graduation in 1995 from the Lorentz College in Arnhem she studied Leisure Management. In 1996 Judith switched between studies, moved to Nijmegen and started with Physical Therapy at the HAN University. She graduated in December 2000, after which she worked as a substitute physical therapist in a nursing home, rehabilitation centre and private practice. Eight months later Judith started to study Biomedical Sciences at the Radboud University Nijmegen Sciences with a major in Human Movement Science. During this study she did a major internship at the Department of Neurology, St. Radboud UMCN. As of October 2003, a minor internship was combined with her first research job at the lab of Professor JHJ Allum in Basel, Switzerland. After graduation in 2004, Judith continued to work in Switzerland for another few months. Then she had various jobs in The Netherlands and in September 2005 Judith started to work as a research assistant at the Pharmacy Department of the Sint Maartenskliniek in Nijmegen. A year later she switched to the Research, Development & Education department where she started her PhD-project on fall risk and medication. This thesis presents the results of that project. In addition, since 2008 Judith participated in the establishment of the CRO Sint Maartenskliniek Nijmegen. As of June 2011, Judith now works as a trial coordinator and project manager at the Office of Science at the Rijnstate Hospital in Arnhem. Amongst others, she offers researchers support in designing, testing and conducting their research in the hospital.